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PYRIMIDINE METABOLISM IN NORMAL MAN STUDIED WITH N^{15} LABELED URACIL

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IN CONTRAST to our knowledge of purine metabolism, which is fairly well understood, our knowledge of pyrimidine metabolism in man is rather limited. The pyrimidines, as well as the purines, are components of such physiologically important substances as nucleic acids, yet the intermediary stages of pyrimidine metabolism have not been established, and the final end-product or products of degradation in man are not known with any degree of certainty.

Some of the earliest work on pyrimidines dates back to about 1901, when Steudel fed several of them to dogs and concluded that they did not contribute to purine metabolism and were not excreted as the intact molecule but were degraded (1, 2, 3). In 1907 Sweet and Levine fed thymine to a dog with an Eck fistula and recovered half in the urine (4). When the same amount was fed in the form of nucleic acid, none could be found in the urine. In 1910 Mendel and Myers concluded that pyrimidines did not become purines, did not metabolize to urea to any degree, and could be recovered in the urine of man when fed (5). When nucleic acid-rich diets were given, pyrimidines were not found in the urine. Wilson recovered pyrimidines quantitatively from the urine of rabbits, but did not find any in the urine of a man given uracil nucleoside. He concluded that the intermediary

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metabolism of nucleic acid involved radical changes in both the purines and pyrimidines before the more complex groups of nucleosides and nucleotides were broken up (6).

In a series of balance experiments, using dogs, Cerecedo concluded that the pyrimidines were converted to urea (7–10). The steps in degradation of uracil to urea and oxalic acid may be considered to be via isobarbituric, isodialuric, formyloxaluric and oxaluric acids as intermediates.

Barnes and Schoenheimer fed isotopic heavy nitrogen (N^{15}) as ammonium citrate to rats and pigeons and found that the nitrogen was incorporated into the body purines and pyrimidines. They concluded that the pyrimidines were involved in the same metabolic processes as the purines and were converted to purines for excretion (11). Thus, uric acid might be derived from the pyrimidines as well as the purines. Plentl and Schoenheimer administered purine and pyrimidines labeled with N^{15} to rats and pigeons and confirmed Cerecedo's work showing that the pyrimidine bases were broken down and excreted as urea (12). This was in marked contrast to other normal tissue constituents which, when fed, were ultimately deposited in the tissues so that they were indistinguishable from material already present.

This report is concerned with the metabolism of uracil labeled with isotopic heavy nitrogen (N^{15}) and the determination of the degradation products in the urine of a normal man. In addition, studies concerned with the incorporation of N^{15} into the patient's hemoglobin were made.

METHODS

Uracil was labeled with isotopic heavy nitrogen (N^{15}). It was synthesized from ammonium nitrate containing 34.9 atom per cent excess N^{15}, in two successive stages.[1] Urea was synthesized from N^{15} ammonia by the copper-catalyzed ammonolysis of diphenyl carbonate (13, 14). The N^{15} urea was then condensed with malic acid to form uracil, labeled at the 1 and 3 positions (15).

The identification and purity of the uracil was checked by melting point determinations and paper chromatography (16, 17). The final purified material contained 32.1 atom per cent excess N^{15}, as determined by analysis with a Nier-type mass spectrometer.

For administration to the patient, 250.6 mg. of N^{15} uracil were converted to the sodium salt, using dilute sodium hydroxide. This was added to 50 cc. of $\frac{1}{6}$ molar sodium lactate (pyrogen-free) and the pH was adjusted to 7.2 with dilute hydrochloric acid. The solution was sterilized by filtration through a Seitz filter and made up to a volume of 200 cc. with sterile $\frac{1}{6}$

[1] The N^{15} labeled ammonium nitrate used in these studies was purchased from the Eastman Kodak Company, Rochester, N. Y.

molar sodium lactate. This was freshly prepared and given intravenously over a thirty-minute period.

The subject was a normal male. He was started on a low purine diet two days prior to the experiment and maintained on this until the end of the period of observation. A 24-hour urine was collected as a control and then the 250.6-mg. dose of N^{15} uracil was administered. No untoward effects from the infusion were noted. Urine samples were collected over periods of eight, twenty-four, forty-eight and seventy-two hours following the infusion.

All urines were preserved with a small amount of toluene and kept in the refrigerator. Quantitative urea, uric acid, and total nitrogen determinations were carried out on all samples of urine. Blood counts and urinalyses gave normal results. The blood chemistry included the determination of nonprotein nitrogen, urea nitrogen, uric acid, total plasma proteins, albumin and globulin, both before and after the administration of uracil; all values were found to be normal. Blood samples were drawn at ten-minute, 24-hour, 48-hour and 72-hour intervals. The erythrocytes were separated from the plasma by centrifugation and washed three times with physiologic sodium chloride. Hemoglobin was purified by the method of Drabkin (18) and set aside for N^{15} determination.

Urea was isolated from each sample of urine as the xanthydrol derivative and purified by repeated crystallizations (19). Uric acid was isolated and purified from each urine according to the method of Geren *et al.* (20). All samples of isolated urea, uric acid and hemoglobin were submitted to Kjeldahl digestion. In addition, 1.0 cc. of urine from each specimen was digested. All of the digested samples were then distilled into dilute sulfuric acid and prepared for analysis of isotopic abundance of N^{15} in the mass spectrometer (21).

RESULTS

The normal atom per cent N^{15} of biologic nitrogen was obtained from control values of the patient's urinary urea, uric acid and total nitrogen. In addition, the N^{15} abundance of urinary urea of another normal person was determined. These values are listed in Table 1. The average value was 0.374 atom per cent N^{15}, with a standard deviation of ± 0.003 atom per cent. The atom per cent N^{15} was calculated from the isotope ratio obtained from the mass spectrometer

The isotopic abundance of N^{15} of each sample of urinary urea, uric acid and total nitrogen following the injection of labeled uracil is presented in Table 2. The atom per cent excess is the increase of N^{15} over the normal abundance found in biologic nitrogen, as determined from the control samples. Figure 1 is a composite of the urinary excretion of N^{15} as total nitrogen, urea and uric acid over the 72-hour period.

The data demonstrate that the greater portion of the uracil was metabolized to urea and excreted as such. During the first eight hours the atom per cent excess N^{15} of the total nitrogen was higher than that of the urea. However, from then on, this pattern reversed itself, and the N^{15} abundance was higher in the urea fraction and continued higher until the

TABLE 1. THE ABUNDANCE OF N^{15} IN VARIOUS COMPOUNDS OF THE URINE FROM NORMAL MAN

Type of nitrogen	Atom per cent N^{15}
Total	0.374
Total	0.374
Total	0.373
Total	0.373
Urea	0.376
Urea	0.376*
Uric acid	0.372
Average	*0.374*

* Another normal person.

end of the experiment. This was interpreted to mean that during the first eight hours some other substance or substances containing N^{15} in greater abundance than that in the urea, was excreted, and hence served to increase the total N^{15} abundance over that found in the urea fraction. If urea had been the only N^{15}-containing substance excreted in the total nitrogen fraction during the first eight hours, its N^{15} content would have been higher, for obviously the total nitrogen fraction contained other nitrogenous substances of which the normal nitrogen (N^{14}) content would serve to dilute the heavy nitrogen of the urine. After eight hours the N^{15} in the non-urea substance or substances was not significant, and the abundance of N^{15} was higher in the urea than in the total nitrogen.

As would be expected, there was a progressive decrease with time in the excretion of N^{15} in both the total nitrogen and urea fractions. Heavy nitrogen was still being excreted as urea seventy-two hours after administration, but in an exceedingly small amount. According to our calculations, only about half (53 per cent) of the administered heavy nitrogen was excreted by the end of the experiment.

Table 2 shows that the atom per cent N^{15} did not increase above the

TABLE 2. EXCRETION OF N^{15} AS UREA, URIC ACID AND TOTAL NITROGEN IN THE URINE OVER A 72-HOUR PERIOD AFTER THE INTRAVENOUS ADMINISTRATION OF N^{15} URACIL TO A NORMAL MAN

Time (hrs.)	Total nitrogen, N^{15}				Urea nitrogen, N^{15}				Uric acid, N^{15}			
	Atom %	Atom % excess	N^{15} (mg.)	Per cent of dose	Atom %	Atom % excess	N^{15} (mg.)	Per cent of dose	Atom %	Atom % excess	N^{15} (mg.)	Per cent of dose
Control	0.374	0	0	0	0.376	0	0	0	0.372	0	0	0
8	0.523	0.149	3.88	19.60	0.486	0.110	2.51	13.0	—	—		
24	0.434	0.060	4.48	23.20	0.440	0.064	4.25	22.0	0.372	0	0	0
48	0.389	0.015	1.61	8.40	0.403	0.027	2.52	13.0	0.371	0	0	0
72	0.379	0.005	0.49	2.54	0.385	0.009	0.80	4.11	0.372	0	0	0

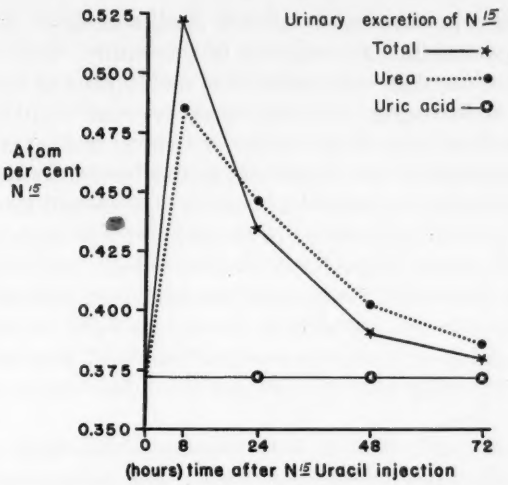

FIG. 1. The urinary excretion of N^{15} administered intravenously in the form of labeled uracil to a normal man. The atom per cent N^{15} found in urinary total nitrogen, urea and uric acid is shown throughout the 72-hour course of study.

normal abundance in any of the samples of uric acid that were analyzed. The atom per cent N^{15} of all uric acid samples was the same as that in the controls. This indicates that the uracil did not enter the pathway of purine metabolism.

TABLE 3. ATOM PER CENT N^{15} OF HEMOGLOBIN FROM A NORMAL PATIENT, FOLLOWING THE INTRAVENOUS ADMINISTRATION OF N^{15} URACIL

Time	Atom per cent N^{15}	Atom per cent excess N^{15}
Control	0.380	0
10 min.	0.378	0
24 hrs.	0.376	0
48 hrs.	0.378	0
72 hrs.	0.378	0

Table 3 shows that none of the N^{15} was incorporated into the patient's hemoglobin during the 72-hour period of observation. The atom per cent excess was zero in all samples, including the one taken ten minutes after completion of the infusion of uracil.

DISCUSSION

The data demonstrate that the pyrimidine base, uracil, is largely metabolized to, and excreted as urea in the normal human. This confirms in

man what Cerecedo showed by balance studies in dogs. Although uracil was the only pyrimidine investigated in this study, there is evidence to show that one of the final end-products of metabolism in man of the other two naturally occurring pyrimidine bases, cytosine and thymine, is also urea. Cerecedo concluded that the latter two, as well as uracil, were excreted as urea in dogs (7, 10). Plentl and Schoenheimer found that all three pyrimidine bases were converted to urea in pigeons and rats (12). Indeed, the latter workers found only urinary ammonia and urea to contain appreciable N^{15} following administration of labeled uracil and thymine to rats. In view of the fact that the present investigation showed urea to be a major product of uracil degradation, it may be valid to conclude that in man cytosine and thymine are similarly metabolized. Several of their intermediate reactions may well be different, but their major end-product is most probably urea.

It must be emphasized that all conclusions drawn refer only to the metabolism of exogenous pyrimidine bases. The endogenous pyrimidines possibly undergo the same catabolism, but this cannot be stated from the information at hand. Exogenous pyrimidines are not incorporated into tissue nucleic acid in pigeons or rats. They are immediately broken down to their end products (11). This is unlike other normal tissue constituents such as amino acids, or fatty acids. The addition of most normal tissue constituents to the diet results in their becoming part of the body tissues, so that one is unable to distinguish between exogenous and endogenous material in the body pool, without labeling procedures. It is difficult to understand why the pyrimidines differ so much in this respect. Of the two purine components of nucleic acid, adenine and guanine, only the former becomes part of tissue nucleic acid when fed. Guanine acts like the exogenous pyrimidine bases, in that it does not become incorporated into the tissue nucleic acid but is immediately metabolized to its end-product.

The uracil was given intravenously in order to avoid the influence of the alimentary tract. Geren *et al.* found that when isotopic N^{15} uric acid was given intravenously to a man, it was excreted as such in the urine. However, when given by mouth, it was degraded to urea (20). They felt that this difference may have been due to degradation by bacterial action in the intestine. It was believed that intravenous administration would eliminate such "artifacts." It also seemed that this would more nearly simulate the conditions under which the endogenous pyrimidines are metabolized once the catabolic phase begins.

The data indicate that during the first eight hours a fraction of the uracil was excreted as some other product in addition to urea. This probably accounts for the previous conflicting reports on pyrimidine metabolism. Some have claimed that uracil is excreted unchanged when fed, whereas

others contend it is metabolized. Mendel and Meyers concluded that it was not metabolized, but was excreted quantitatively and unchanged for about twelve hours following oral administration in man (5). Wilson also recovered uracil from the urine of rabbits after oral administration (6). Our data appear to resolve these conflicting reports, for in all probability the N^{15}-containing substance excreted during the first eight hours in addition to urea, was a small quantity of unchanged uracil. The uracil then is largely metabolized to urea and only minutely excreted unchanged. Since the substance was not identified, this cannot be definitely known. The calculations reveal that about 65 per cent of the total N^{15} excreted during the first eight hours was in the form of urea, indicating that the major portion of the uracil was metabolized during this early period. The data also show that 53 per cent of the administered N^{15} was accounted for in seventy-two hours.

Despite the apparent close association between the purines and pyrimidines, none of the uracil was metabolized to uric acid. The data support most of the earlier work, from which it was concluded that the pyrimidines do not metabolize to purines and do not have a final common pathway with the latter. Although these two groups of compounds are closely related structurally and are component parts of the same nucleic acid molecule, their metabolism is different. During purine metabolism the ring structure remains intact and all changes occur on the outside of the ring, with the final formation of uric acid. However, when the pyrimidines are metabolized, the ring breaks open and the basic structure is no longer maintained but goes on to form urea. It would seem that more energy should be required to break open a pyrimidine ring than merely to substitute atoms on the outside of the purine nucleus. It would then appear that there are more possibilities for abnormal metabolites to occur during pyrimidine metabolism than during the metabolism of purines. It remains to be determined whether or not abnormal pyrimidine metabolites occur in various pathologic states. A study of pyrimidine metabolism in diabetes mellitus is in progress.

According to earlier work, pyrimidines are not normally found in the urine. Yet when free pyrimidines are given, small quantities appear in the urine (4, 5, 6). When equivalent quantities of pyrimidine base in the combined form (nucleic acid, nucleotide, nucleoside) are administered, none appears in the urine (6). Either catabolism and excretion differ in the two forms (combined and free) or, when metabolized in the combined form, only small amounts are set free slowly, and thus the renal threshhold is not exceeded. When free pyrimidine is given rapidly, as in this study, the renal threshhold is exceeded and some appears in the urine.

A recent observation linking pernicious anemia and pyrimidine metabo-

lism has been reported. Vilter *et al.* produced remissions in pernicious anemia by giving large oral doses of uracil for ten days (23). They concluded that folic acid, liver extract and vitamin B_{12} act by facilitating the formation and utilization of purines and pyrimidines. Riddle showed that the urinary uric acid excretion increased during remissions of pernicious anemia induced by liver (24). This was interpreted as indicating an increase in nucleic acid metabolism in the maturation of the red cell. We thought it would be of interest to see whether or not any of the N^{15} administered as uracil would appear in the patient's hemoglobin. The data show that the N^{15} was not incorporated into the hemoglobin over a three-day period (Table 3).

The atom per cent of N^{15} of the total nitrogen, urea and uric acid nitrogen from the control urines was consistently higher than that of tank nitrogen. The observation was checked in more than 20 determinations, and the atom per cent N^{15} of normal biologic nitrogen always exceeded that from the tank by 0.005. This is in agreement with the findings of others (20). Further studies on the N^{15} enrichment of biologic nitrogen are in progress.

SUMMARY

The pyrimidine, uracil, was labeled with isotopic heavy nitrogen (N^{15}) and given intravenously to a normal man. It was degraded to urea and excreted in the urine almost entirely in this form. A small portion was excreted as an unidentified substance containing N^{15}. It is believed that the unidentified substance excreted in the urine was unchanged uracil. Reasons for this conclusion are discussed.

None of the isotopic uracil was metabolized to uric acid, indicating that purine and pyrimidine metabolism in man are separate and do not have a final common pathway. This indicates that during the degradation of these substances the pyrimidine ring is broken, whereas the purine ring remains intact. N^{15} from the isotopic uracil was not incorporated into the patient's hemoglobin during the three-day period of the study.

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STUDIES ON TOXEMIA OF PREGNANCY: EFFECT OF DESOXYCORTICOSTERONE ACETATE (DCA) ON HEMODYNAMICS AND ELECTROLYTE BALANCE OF NORMAL PREGNANT WOMEN*

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THE role of desoxycorticosterone acetate (DCA) in the genesis of hypertension has received considerable attention. DCA may produce hypertension by its effect on electrolyte metabolism or by an action on the kidney (1). The symptoms of edema, hypertension and proteinuria characteristic of toxemia of pregnancy are similar in some respects to those observed in DCA overdosage in animals (2–5). This similarity has led to the hypothesis that toxemia of pregnancy may be caused by excessive secretion of DCA or DCA-like substances by the placenta or the adrenals (2–5). That the elevated blood pressure of toxemia of pregnancy may be humoral in origin is suggested by Dexter's observation (6) that renin is present in the blood. Also, ganglionic blockade with tetraethylammonium chloride (TEAC) in patients with toxemia does not produce the pronounced drop in blood pressure observed in normotensive pregnant women (7, 8, 9). This fact augments the evidence suggesting the presence of a humoral agent in toxemia and provides helpful means for evaluating early changes in the direction of toxemia.

The present study was undertaken in order to determine if the short-term administration of DCA to normotensive pregnant women would reproduce any of the physiologic changes observed in toxemia of pregnancy.

METHODS

Five women in the last trimester of pregnancy were selected from the prenatal clinic on the basis of a normal prenatal course, with no evidence of renal, cardiovascular or endocrine disease. Four of them had, on repeated tests, a typically normal response to ganglionic blockade with

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TEAC. Patient 5 was clinically normal in all respects but her blood pressure failed to fall on administration of TEAC, as in the case of patients with toxemia of pregnancy.[1]

The experiments were carried out in the hospital so that the patients could be kept in bed for the few days of study. A regular hospital diet, supplemented by 9 grams of sodium chloride daily, was provided and the patient's fluid intake was measured. The study consisted of three consecutive periods. The first period (two to four days) served as a control. DCA (Percorten[2]) was given by intramuscular injection twice daily for the three to four days of the second period. The third period, a post-treatment control, varied in length from one to four days. Pertinent data are given in Table 1.

TABLE 1

Patient	Age (yrs.)	Length of gestation (weeks)	No. days control	No. days DCA	No. days post-treatment control	DCA dose (mg./day)
1. E.P.	21	32	4	4	2	20
2. M.T.	20	34	3	4	2	30
3. B.O.	22	37	3	3	2	20
4. V.B.	28	36	2	3	1	10
5. T.B.	23	31	4	3	4	20

The following measurements were made:

1. The patient's weight was recorded at the same time each day; blood pressure (sphygmomanometer) and pulse rate were measured at four-hour intervals by the same observer with the patient in the supine position. Electrocardiograms were obtained daily and heart size was estimated by teleoroentgenograms at one- to two-day intervals. The cardiac output was measured by a high frequency ballistocardiograph every other day (10).

2. The tetraethylammonium chloride (TEAC) test was performed by the intravenous injection of 400 mg. of the drug, according to the method described elsewhere (7–9). The lowest blood pressure value obtained within the first ten minutes after the injection was termed the TEAC "floor."

3. Twenty-four-hour urine specimens were collected throughout the study. Aliquots were frozen for corticoid and electrolyte analyses; acidified and refrigerated for creatinine and 17-ketosteroid analyses. Routine urinalyses were performed daily.

[1] At the time of this study, lack of blood pressure fall after TEAC was not regarded as a diagnostic sign of vascular disease. Since this study was begun, a large number of observations have been accumulated which indicate that an elevated TEAC "floor" in an otherwise normal pregnant patient suggests an underlying hypertensive renal disease (9).

[2] Percorten was furnished through the courtesy of Ciba Pharmaceutical Products, Summit, N. J.

4. Plasma potassium, sodium and chloride concentrations were determined at least daily, and CO_2, urea nitrogen and uric acid were measured on alternate days.

Sodium and potassium analyses were carried out by means of a Varnay-Weichselbaum flame photometer. Urea nitrogen, chloride and carbon dioxide concentrations in plasma were measured by methods currently in use at the Cincinnati General Hospital. Creatinine was measured by the picric acid procedure (11); 17-ketosteroids by continuous hydrolysis and extraction with carbon-tetrachloride and the aqueous alkali colorimetric procedure (12–14). The freely water-soluble formaldehydogenic corticosteroids were assayed following benzene-water partitioning of a chloroform extract made from urine at a pH of 1.5 (15, 16). The significance of results was calculated by a non-parametric median test (17) and probabilities were computed by the exact method described by Rider (18).

Placentae and adhering parts of the decidua were examined in the department of pathology for the presence of infarcts and atherosis (19).

RESULTS

The data obtained from the study of the 5 patients are given in Figures 1–5. The 4 patients with normal control TEAC responses are presented together, but the 1 who was abnormal in this respect (Patient 5) is discussed separately

A. *Normal patients*

Blood pressure and TEAC responses. The administration of DCA evoked no significant change in the resting blood pressure or pulse rate. There was no change in the blood pressure response to ganglionic blockade with TEAC. The 4 patients continued to present the low TEAC "floor" characteristic of normal pregnancy near term.

Cardiac output. There was no significant change in the cardiac output in any of the subjects. Daily variations of 0.5 to 1.0 liter were observed in some instances, but these were without relationship to the administration of the drug.

Heart size and electrocardiograms. The teleoroentgenograms of the chest and the electrocardiograms did not indicate any significant cardiac changes.

Weight. There were no appreciable variations in weight during the period of the study.

Water balance. There was no consistent change in water balance, as estimated from fluid intake and volume of urine excreted.

Renal function. No proteinuria, glycosuria or hematuria occurred. There were no changes in the levels of plasma CO_2 or urea nitrogen.

Electrolytes. There was no indication of retention of sodium or loss of potassium, as judged by analysis of the plasma and the urine. The changes in chloride seen in the figures are not regarded as significant.

Excretion of 17-ketosteroids and corticosteroids. The excretion of 17-ketosteroids in Patients 1 and 2 was apparently not affected by the adminis-

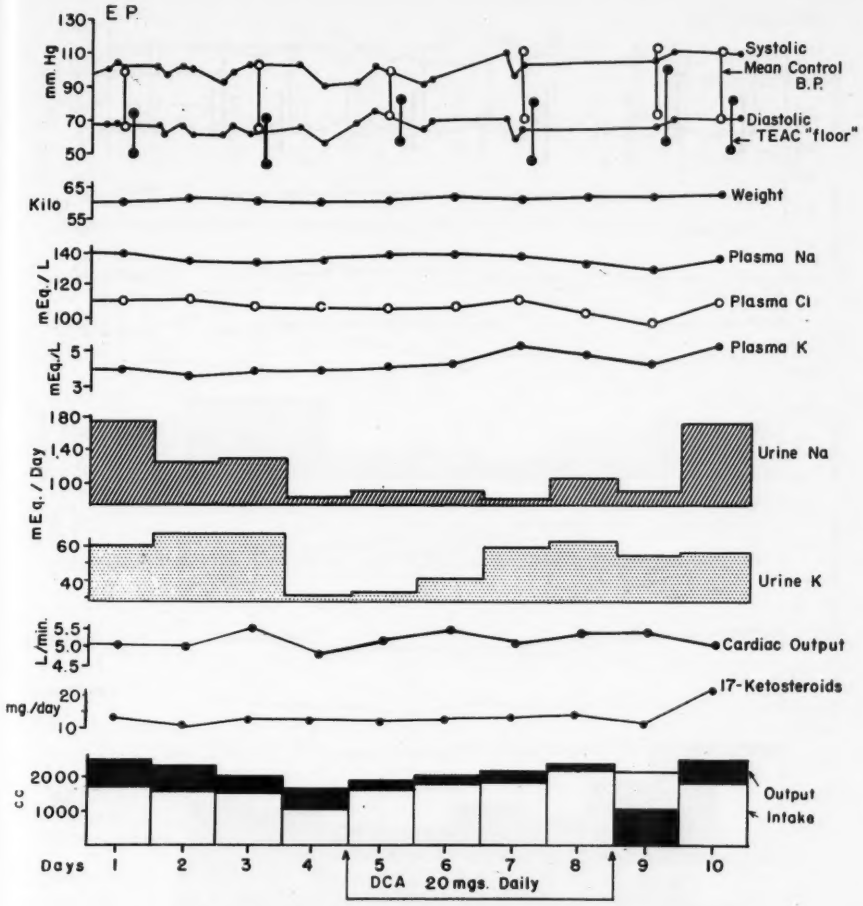

FIG. 1. Hemodynamics, water and electrolyte balance in Patient 1.

tration of DCA. No further analyses for 17-ketosteroids were conducted. In Patient 2 the corticosteroid excretion appeared to be suppressed by the DCA treatment, to an extent which can probably be regarded as meaningful ($P = .016$). There are reports (20) that DCA causes an increased excretion of chemically determined corticosteroids. This could be explained by the excretion of some of the injected compound, which would be more soluble in benzene than in water (21). The benzene-water partitioning performed in the analysis reported here would have removed most of the benzene-soluble steroids.

Delivery. The patients were discharged from the hospital following the

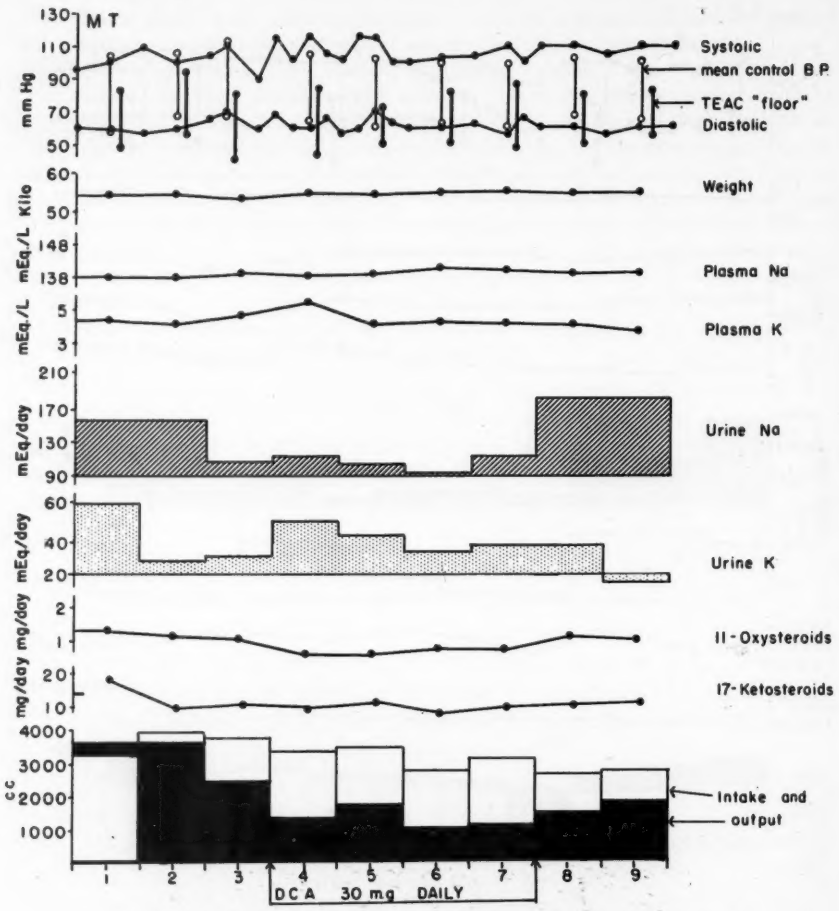

FIG. 2. Hemodynamics, water and electrolyte changes in Patient 2.

experiment and later delivered normal babies spontaneously at term. There was no evidence of decidual atherosis or placental infarcts comparable to those seen in toxemia.

Four to ten months later, these patients showed no abnormalities. Patient 4 has had a subsequent normal pregnancy and delivery.

B. *Patient 5*

Abstract of case history:

T.B. was a 22-year-old Negress, grav. 2, para 0. She was admitted from the prenatal clinic on April 18, 1951, at 28 weeks' gestation, because of slight vaginal bleeding. There

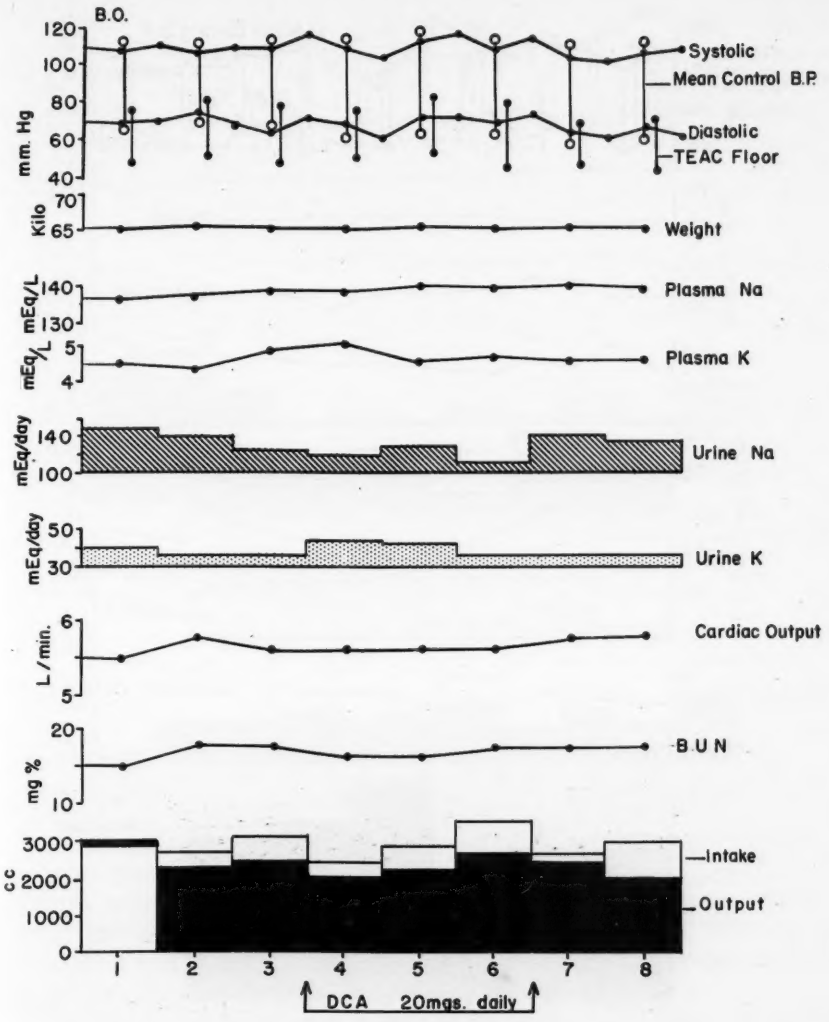

FIG. 3. Patient 3.

had been a spontaneous abortion at home in 1948. In February 1950 she was treated in the hospital for bronchopneumonia, which was uncomplicated and from which she made a satisfactory recovery. There was a moderate hypochromic anemia, which responded to oral iron therapy. Blood pressure, weight gain and urine were found to be normal at regular prenatal visits. Intermittent vaginal bleeding had occurred for two weeks prior to admission. Physical examination showed a well developed, healthy young woman. There was no edema; blood pressure was 120/82; pulse 90. The size of the uterus was compatible with a 28-week intrauterine pregnancy. The fetus was in vertex position and

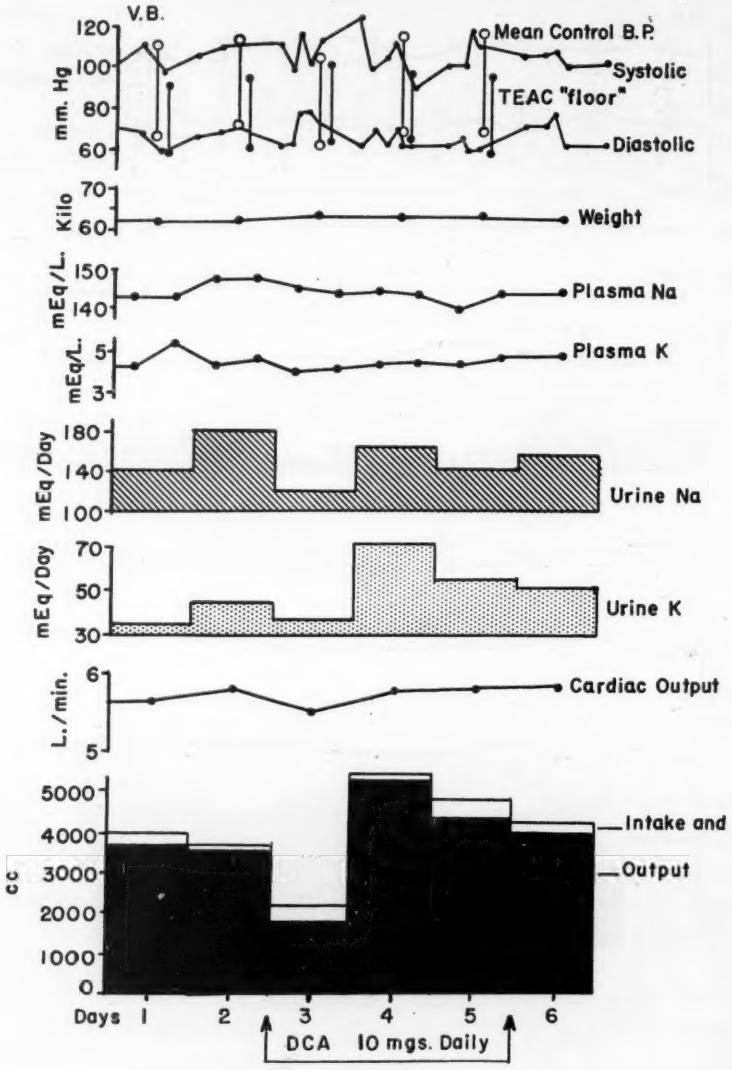

FIG. 4. Patient 4.

had a normal heart rate. Speculum examination showed cervical erosion with bleeding originating from the posterior cervical lip. The bleeding subsided, and the patient was then considered suitable for the DCA study.

This patient had TEAC "floors" which were regarded as somewhat above normal, but otherwise she was apparently in good health. Later

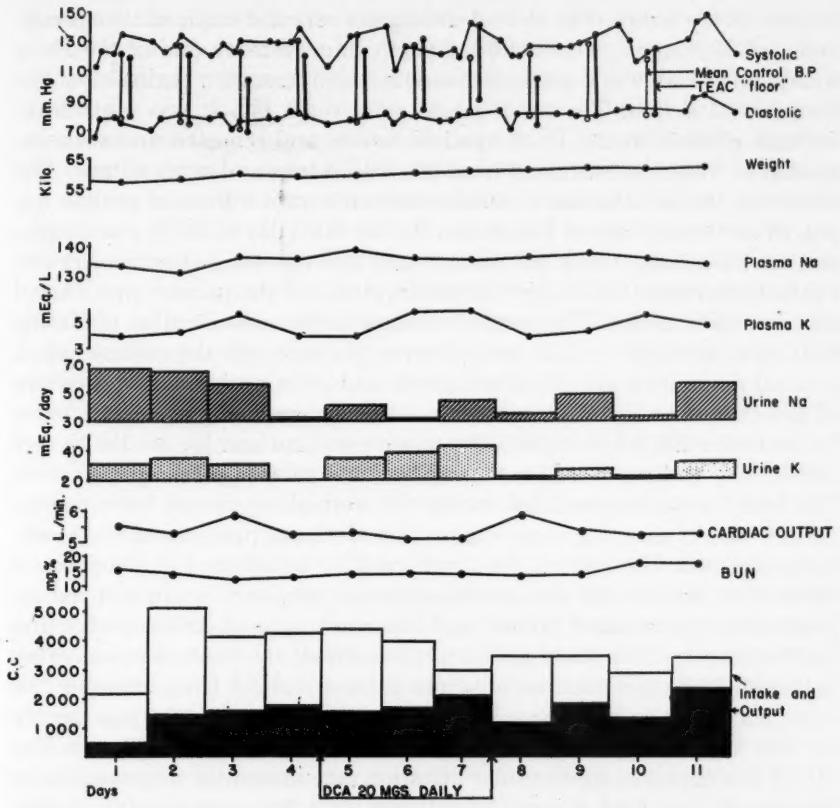

FIG. 5. Patient 5.

events, which revealed that she probably had undetected impairment of renal function, led to the discontinuation of DCA on the third day of treatment and the substitution of a low-sodium regimen for the relatively high sodium intake used during the study.

During the control period the blood pressure ranged from 112 to 138 systolic and 64 to 82 diastolic. The highest pressure after treatment was 146/92. The response to TEAC remained abnormal during the first day of DCA administration, in that there was no fall of blood pressure (Fig. 5). On the second and third days there was a rise in blood pressure when TEAC was administered, instead of the usual fall. The cardiac output showed insignificant changes. A roentgenogram of the chest showed a slight increase in the transverse diameter of the heart on the first control day, which was ascribed to the elevated diaphragm; it did not change during

the rest of the study. The electrocardiogram revealed minimal nonspecific myocardial changes, which showed slight improvement during the DCA treatment. There was a steady increase in weight from the beginning of the first control period. The total weight gain was 4 Kg. It was apparently without relation to the DCA administration, and reflected an excess retention of water, as estimated from the fluid intake and urine output. The urine was free of albumin or cellular elements until a trace of protein appeared on the first day of treatment. On the third day of DCA administration, ankle edema, frank proteinuria and microscopic hematuria became evident; therefore the study was interrupted and the patient was started on a low-sodium diet. There was no change in the concentration of plasma CO_2, urea nitrogen or uric acid. During the next ten days there was a gradual diminution of edema, hematuria and proteinuria. The fluctuations of the plasma sodium and potassium levels shown in Figure 5 bore no relation to the DCA treatment. The urinary sodium was low on the second control day and remained low during the remainder of the hospitalization. The blood pressure remained within the normal range and there was no further weight gain; a gradual diminution of edema, proteinuria and hematuria occurred. The patient was discharged, to be followed in the prenatal clinic. One month later rehospitalization was necessary because of the appearance of generalized edema and the recurrence of severe proteinuria and hematuria. The blood pressure was normal; the heart was somewhat enlarged. The concentration of serum protein was 5.5 Gm., albumin 2.05 Gm., globulin 3.4 Gm., uric acid 6 mg. and urea nitrogen 52.5 mg. per 100 cc. The concentration of CO_2 was 29.7 mEq./L. The renal plasma flow (PAH clearance) and glomerular filtration rate (mannitol clearance) were abnormally low (234 cc. and 33 cc./min./1.73 M^2, respectively). Within one week anuria developed, with progressive uremia. The pregnancy was interrupted, with no beneficial effect. Treatment of the anuria was unsuccessful, and on the twelfth day of anuria the patient died with pulmonary edema and cardiac failure. Permission for autopsy was denied. The clinical impression was that the patient had an acute exacerbation of a chronic glomerulonephritis, and that the DCA administration did not bear a causal relationship to the renal disorder.

DISCUSSION

The data show that the effects of DCA and salt, in the amounts used, failed to duplicate any of the symptoms or signs of toxemia of pregnancy in normal pregnant women. The occurrence of edema, proteinuria, hematuria and renal failure in a single patient cannot be attributed to the DCA treatment.

The fact that toxemia of pregnancy may develop in previously normo-

tensive women permits the hypothesis that in this disease there may be overproduction of DCA or DCA-like hormones which are normally elaborated during pregnancy. Therefore, the amount of hormone given to the patients in the present study may not have been sufficient to produce any significant changes characteristic of toxemia. This possibility, however, seems unlikely, since doses of DCA as high as 60 mg. daily have been given for several days to normotensive pregnant subjects without producing significant effects (22). Although some of the animal experiments performed with DCA and salt have succeeded in producing pathologic changes which somewhat resemble those of toxemia and other hypertensive states (23, 24), most of the experiments in humans with intact adrenals have failed to lead to a hypertensive response, even when enormous quantities of salt and large doses of DCA were employed (25, 26).

Of interest is the decreased corticosteroid excretion demonstrated in the one patient in whom this measurement was made. 'This seems to indicate that the dose of DCA given was adequate to suppress spontaneous adrenal activity but does not establish whether or not it was sufficient to elevate the total circulating hormone in the body.

Lloyd and his associates (27) have recently shown that the excretion of corticosteroids, particularly the poorly-water-soluble material, is increased in toxemia of pregnancy. Although this finding suggests the presence of certain adrenocortical activity, it doesn't help to establish whether or not overproduction of DCA-like substances is responsible for the toxemia of pregnancy.

Tobian (28) has reported that the excretion of 17-ketosteroids in toxemia of pregnancy is increased, particularly when edema is present. This observation is not in accord with unpublished results from our laboratories. Measurement of these steroids in a large number of normal pregnant and toxemic subjects failed to show any significant difference (29).

Modifications in the response to ganglionic blockade by the administration of ACTH plus salt have been reported in normotensive nonpregnant and hypertensive subjects (30, 31). It was suggested that this hormone may increase the humoral component of blood pressure. The present data show that DCA, in the dosage given, failed to produce any change in the response to TEAC; thus the changes observed after ACTH may not be caused by stimulation of secretion of DCA or DCA-like hormones.

Other hypotheses which could be advanced are: 1) patients with toxemia of pregnancy have limited ability to detoxify or metabolize endogenous steroids, or 2) toxemic subjects are oversensitive to the amounts usually present during normal pregnancy. Since the present data cannot rule out these possibilities, further investigations are needed in order to substantiate either hypothesis.

SUMMARY

1. The effect of desoxycorticosterone acetate (DCA) on the hemodynamics and electrolyte balance of normal pregnancy was studied in 5 normotensive subjects.

2. No changes in the resting blood pressure level and blood pressure response to tetraethylammonium chloride (TEAC) were observed. The excretion of electrolytes showed some variation, which was not related to DCA administration. The excretion of 17-ketosteroids was unchanged but that of corticosteroids showed some decrease during DCA administration.

3. In the dosage given, DCA and salt failed to induce any of the changes seen in toxemia of pregnancy.

4. One patient, clinically normal at the beginning of the study except for her response to TEAC, died of renal failure six weeks following the use of DCA.

Acknowledgments

We wish to thank Dr. Pearl M. Zeek for the pathologic examination of the placentae and deciduae; Dr. John Braunstein for the cardiac output determinations; and Gabriel Alverson, R. Phillis Fox, Gwen Prior and R. Suyemoto for valuable assistance in the laboratory analyses. The Vernet Equipment Foundation furnished the flame photometer.

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PROGESTERONE METABOLISM. II. PREGNANEDIOL EXCRETION FOLLOWING ORAL, SUBLINGUAL AND PARENTERAL ADMINISTRATION OF PROGESTERONE

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THE continuing accumulation of data serves to emphasize the quantitative relationship between progesterone and its urinary metabolite, pregnanediol. Refinements of techniques for the determination of this substance have served to make more constant the values recovered in the urine following the administration of progesterone to human subjects. Although figures quoted vary from zero to as high as 48 per cent of administered progesterone recovered as pregnanediol, more recent findings indicate that in the nonpregnant female and in the male approximately 10.0 per cent of exogenous progesterone can be recovered in the urine as pregnanediol.

Using the method of Chaney and McKee (1) for the determination of free pregnanediol, we have reinvestigated this problem with particular reference to the influence of the method of administration on the quantity of pregnanediol recovered.

MATERIALS

Subjects used in this study consisted of apparently normal young women, adult males, and women who previously had had a total hysterectomy with bilateral salpingo-oophorectomy. Progesterone was administered in three general ways: progesterone-in-oil[1] intramuscularly, progesterone lingusorbs intrabuccally, and progesterone lingusorbs orally.

METHODS

In the males and the oophorectomized females, a base line of pregnanediol excretion was determined and progesterone administered in the dosage indicated. When pregnanediol excretion had returned to the base line, pro-

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[1] Progesterone-in-oil and Progesterone lingusorbs were generously supplied by Ayerst, McKenna & Harrison, Ltd.

gesterone was readministered by one of the other routes until the study was completed.

In the case of the young females with cyclic menstruation, pregnanediol was determined on the day following the completion of the menstrual period and progesterone was given on the following day. Twenty-four-hour urines were collected until the pregnanediol content had reverted to the base line. Each of the parts of the study was performed on consecutive months in the manner described.

All subjects collected complete 24-hour urine specimens without preservative during the study period and the pregnanediol was determined by the method of Chaney and McKee (1).

RESULTS

As pointed out in a previous communication (2), it has not been possible to obtain a zero reading using this colorimetric method. For this reason, we have averaged the values for pregnanediol obtained during the so-called baseline period and subtracted this from the total quantity of pregnanediol obtained during the period of its excretion, to arrive at the probable true value.

The results obtained show a remarkable constancy for all groups of subjects studied and for all three routes of administration. Although 100 mg. of progesterone was the dosage commonly employed, it was necessary

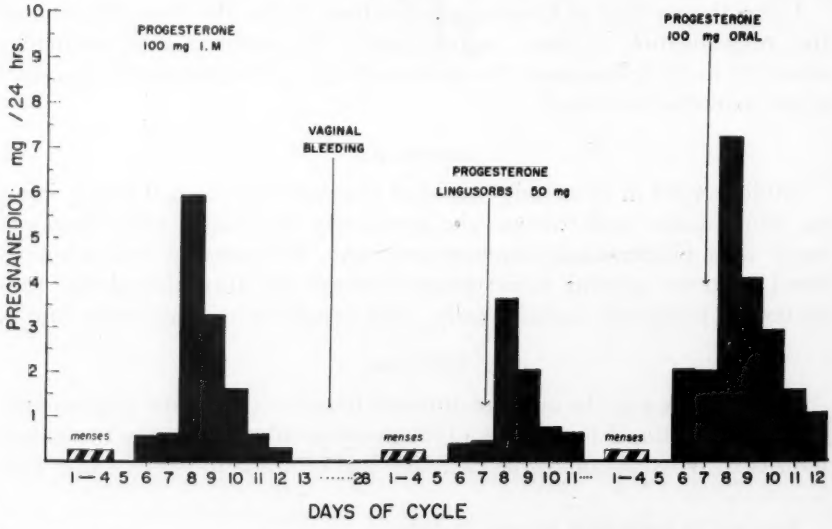

FIG. 1. A 26-year-old, single female (P-0, G-0) with no known abnormalities of the menstrual cycle.

to reduce this to 50 mg. in the case of the young females, in order to avoid withdrawal bleeding (Figs. 1 and 2). Regardless of the dose employed, the conversion rate appeared to remain the same.

In the early days of pregnanediol studies, some investigators were unable to demonstrate that progesterone administered to a subject could be

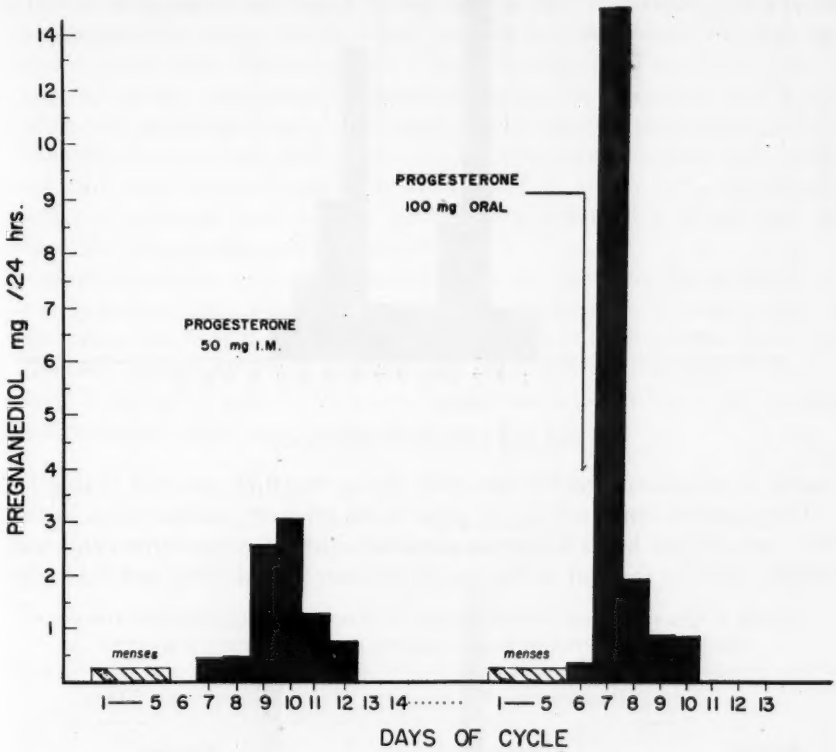

FIG. 2. A 23-year-old, married female (P-III, G-III) with no known abnormalities of the menstrual cycle.

recovered in the urine as pregnanediol (3). Continuing efforts, however, revealed that exogenous progesterone was converted to pregnanediol in both males and females and could be isolated from the urine (4–9). Most of the figures recently reported indicate that the quantity of pregnanediol recovered represents about 10 per cent of the administered progesterone. Our findings serve to substantiate this impression. The lowest figure obtained was 6.9 per cent in a male subject following intramuscular administration (Fig. 3) and the highest figure was 15.2 per cent in a young female after oral administration (Fig. 2). However, the average for the three

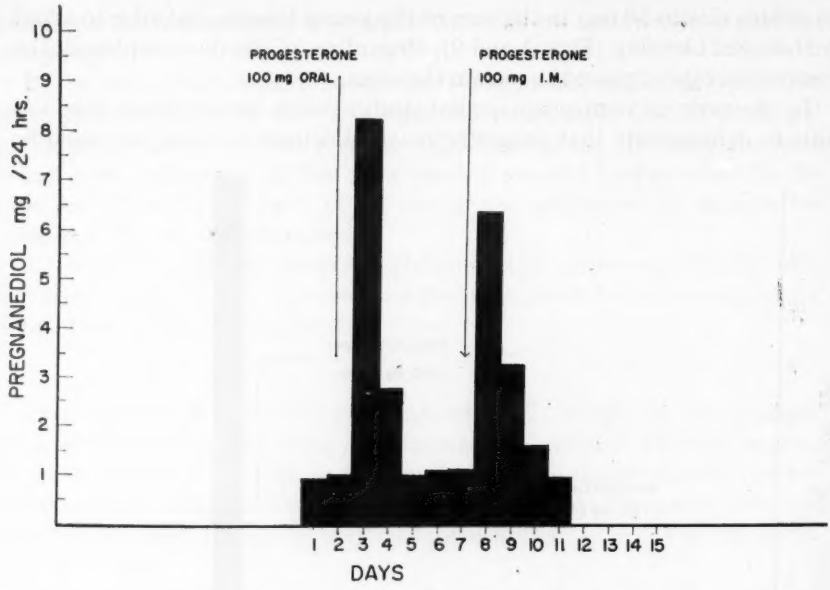

FIG. 3. A 35-year-old, adult male.

routes of administration for the entire group was 9.78 per cent (Table 1).

Pregnanediol appeared in the urine in its greatest concentration in the first twenty-four hours following administration of progesterone and was usually gone by the end of the second 24-hour period. This fact held true

TABLE 1. QUANTITIES OF PREGNANEDIOL (MILLIGRAMS) RECOVERED FOLLOWING THE ADMINISTRATION OF PROGESTERONE IN THE AMOUNTS INDICATED

Subject	Progesterone, 100 mg.			Progesterone, 50 mg.		
	Intra-musc.	Absorbed intra-bucally	Oral	Intra-musc.	Absorbed intra-bucally	Oral
R.C.	9.02	8.59	—	—	—	—
L.E.	—	—	15.2	5.11	—	—
J.E.	8.61	—	8.56	—	4.49	—
L.H.	8.88	13.1	9.73	—	—	—
R.F.	6.90	—	8.52	—	—	—
D.H.	9.50	9.40	11.90	—	—	—
Average % recovered	*8.58*	*10.36*	*10.78*	*10.22*	*8.98*	—
	Overall average recovered—9.78%					

for all three routes of administration. It must be pointed out, however, that the time of administration did not coincide exactly with the end of a given collection period, so the excretion curves are probably weighted in the direction of the second 24-hour period. The average quantity of pregnanediol found in the second 24-hour period after intramuscular administration of progesterone was 3.37 mg. in five determinations. The average following other routes was 2.55 mg. in eight determinations. The fact that the intramuscular administration of progesterone-in-oil was followed by a slightly greater pregnanediol excretion during the second 24-hour period than that found after oral or sublingual administration probably represents the differences in absorption rates. It might be of considerably more interest and value to study the excretion pattern in hourly urine fractions in order to ascertain more exactly the time required for the appearance and then the disappearance of pregnanediol.

Several authors have called attention in the past to a latent period between progesterone administration and the appearance of pregnanediol in the urine. We have not observed this phenomenon during either this study or other studies involving progesterone metabolism. One subject who received 100 mg. of anhydrohydroxyprogesterone failed to reveal any urinary pregnanediol following its administration (Fig. 4).

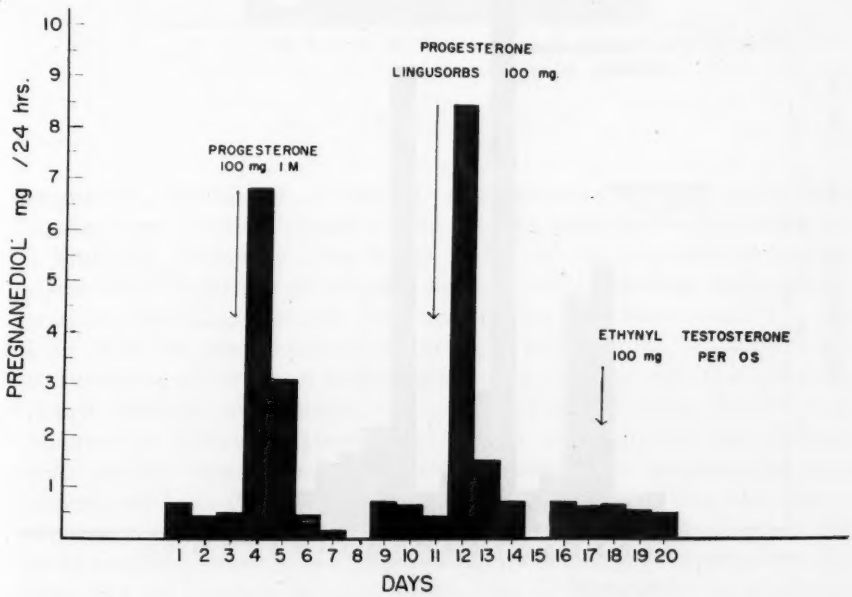

FIG. 4. A 46-year-old female. Hysterectomy and bilateral oophorectomy in 1949.

DISCUSSION

The facts pertaining to the metabolism of progesterone in humans must be deduced from a comparison of the clinical and laboratory data available. In view of the results reported here and elsewhere, it seems that the human subject reduces progesterone to pregnanediol at a fairly constant rate, uninfluenced by its passage through the liver. There does exist, without doubt, sufficient evidence to indicate that the degree of certain physiologic activities of progesterone is altered by varying the route of administration, in spite of this constancy of pregnanediol excretion. Bickers (10) has reported that oral progesterone is effective in producing progestational changes in the estrogen-primed endometrium but slightly higher doses are required to produce effects comparable to those observed after parenteral administration. Greenblatt *et al.* (11) found that withdrawal bleeding was produced in 92.3 per cent of amenorrheal patients treated with oral progesterone alone, indicating that oral progesterone is absorbed and utilized to some extent. In addition, these patients exhibited a rise in basal temperature during the period of administration and pregnanediol was

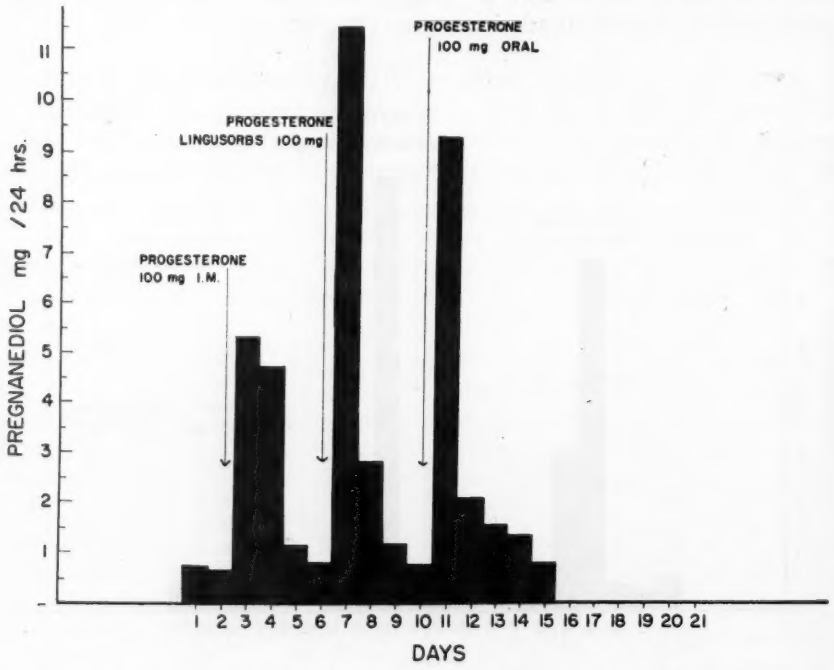

FIG. 5. A 43-year-old female. Hysterectomy and bilateral oophorectomy in 1949.

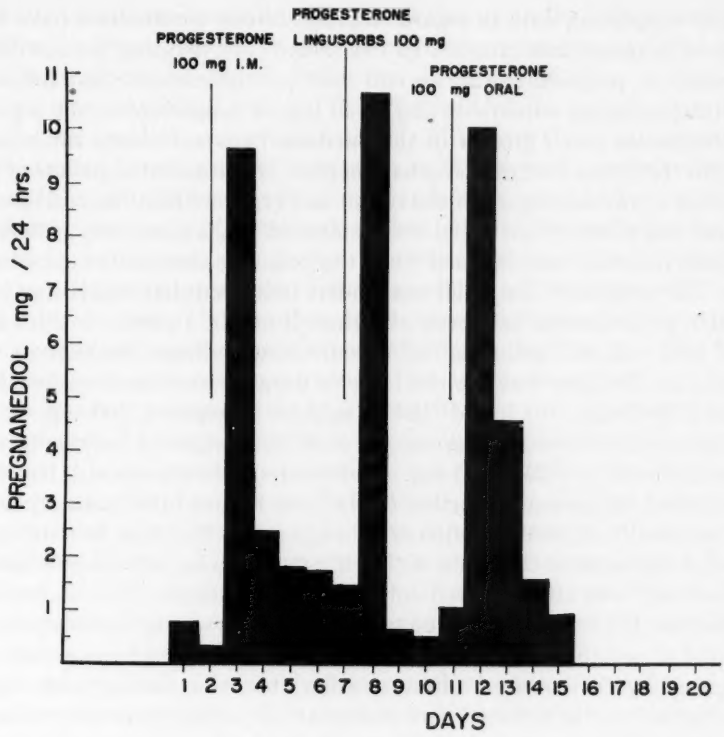

FIG. 6. A 23-year-old, adult male.

excreted in the urine in all cases. In those patients in whom endometrial studies were obtained, progestational changes could not be demonstrated.

From the laboratory, Rogers and McLellan (12) were able to demonstrate small quantities of pregnanediol in the bile following oral administration, suggesting that this reduction process may have occurred in the liver. After the administration of 500 mg. of progesterone by mouth, there was recovery of 3.8 mg. of pregnanediol in the bile drainage. It is apparent that a relatively small proportion is excreted by this route. Recent work reported by Havens, Myerson, and Carroll (13) indicates that patients with chronic hepatic disease convert progesterone to pregnanediol at a higher rate than do normal subjects. One patient receiving 100 mg. of progesterone a day excreted as much as 52.0 mg. of pregnanediol in the urine per twenty-four hours. These authors conclude that chronic liver disease does not interfere with the metabolism of progesterone to pregnanediol, but that metabolism beyond this point is impaired.

Most supporting data in regard to progesterone metabolism have been obtained in animal laboratories. In 1941 Selye (14), utilizing the anesthetic properties of progesterone as an end point, demonstrated that following the intraperitoneal administration of 50 mg. of progesterone, the depth of anesthesia was much greater in the partially hepatectomized rat as compared to the intact controls. Kochakian *et al.* (15) implanted pellets of progesterone in various organs of the rabbit and reported that the endometrial reaction was absent if the pellet was implanted in the mesentery, whereas a four-plus reaction was obtained when the pellet was implanted subcutaneously. The weights of the pellet remainders indicated that nearly five times as much progesterone had been absorbed from the mesenteric site, compared with the subcutaneous site. From these findings, the authors concluded that the liver was the chief site of progesterone inactivation. Masson and Hoffman (16) found that in rabbits it required 200 mg. of progesterone administered by gavage to elicit the degree of endometrial response induced by 0.25 to 0.5 mg. administered subcutaneously. However, the removal of the major portion of the liver reduced the quantity necessary to produce a positive endometrial response to 25.0 mg. As much pregnanediol appeared in the urine of the rabbits following gavage as when the progesterone was administered subcutaneously. Inasmuch as it has been shown that both male and female rabbits convert progesterone to pregnanediol at approximately the same rate as humans, and apparently uninfluenced by the route of administration (17), this finding adds significance to the results reported here in humans in aiding us to determine the importance of pregnanediol in the metabolism of progesterone.

More recent work, using C^{14}-tagged progesterone, has revealed that most of the C^{14} is excreted in the feces and expired air of the rat and the mouse (18). The greatest amount of tissue radioactivity was found in the liver. Grady *et al.* (19) added appreciably to this work by indicating in the rat that the labelled progesterone is carried to the intestine in the bile and that obstruction of the biliary passages results in the appearance of large quantities in the urine. Barry *et al.* (20) substantiated these findings but pointed out that information concerning the fate of progesterone in rodents is not directly applicable to the problem of its metabolism in humans. This observation seems particularly apropos, as neither the rat nor the mouse are known to reduce progesterone to pregnanediol.

There are several other items of interest which have been brought to light as a result of animal studies concerning the metabolism of progesterone. It has been demonstrated that the ability of progesterone to produce its characteristic morphogenetic effects in the rat (atrophy of the adrenals and thymus, and hypertrophy of the uterus) is greatest when administered subcutaneously, whereas its anesthetic properties are greatest when it is

administered intraperitoneally (21). Could this mean that the route of administration determines the proportion of various progesterone metabolites and thereby alters the degree of response of certain specific manifestations of progesterone activity? Leblond (22) showed that the anesthetic properties of pregnanediol and pregnanedione, following their intraperitoneal administration, were greatly enhanced in the partially hepatectomized animal. Injection of pregnanedione subcutaneously into intact animals produced the same degree of anesthesia as that found in the partially hepatectomized ones following intraperitoneal administration. This fact suggests that the anesthetic properties of pregnanedione are, to some extent, destroyed by the liver. The fact that progesterone possesses fewer anesthetic properties, unless injected intraperitoneally where the liver may first begin its degradation, lends credence to our earlier assumptions that metabolites are important in producing the characteristic responses attributed to the parent steroid. That pregnanediol is not the inert and biologically inactive substance it is so commonly claimed to be is suggested by the demonstration of its anesthetic properties. In addition, Hisaw (23) has shown that the concurrent administration of 0.25 mg. of pregnanediol will completely inhibit the ability of 1.5 mg. of progesterone to produce decidua in the castrated rat. This phenomenon appears to be a direct competitive reaction, since increasing the amount of progesterone while keeping the quantity of pregnanediol constant will restore the full decidual reaction.

From an analysis of available data concerning the metabolism of progesterone, it seems a reasonable conclusion that the major portion of this process takes place in the liver. Although the route of progesterone administration materially alters the degree of its physiologic activities, there is no apparent effect on the rate of pregnanediol excretion. Patients with chronic liver disease, following progesterone, appear to excrete more rather than less pregnanediol than normal subjects, possibly reflecting an impairment of the further metabolism of pregnanediol. Such an explanation is certainly more credible than that the diseased liver is metabolizing progesterone to pregnanediol at an increased rate. This suggests that the reduction of progesterone to pregnanediol may occur at a site other than the liver, and that further degradation and other pathways of metabolism are a function of the liver. Each activity or groups of activities assigned to the steroid progesterone may represent activities of its various metabolites, and failure to consider this possibility may result in misinterpretation of data obtained in studying various routes of progesterone administration.

It seems fairly conclusive that urinary pregnanediol is not indicative of those physiologic activities of progesterone with which we are most familiar.

SUMMARY

1. The excretion of urinary pregnanediol is remarkably constant following the oral, sublingual, or parenteral administration of standard quantities of progesterone to males, young females, or oophorectomized and hysterectomized females.

2. A review of some of the present-day facts concerning the metabolism of progesterone seems to indicate that most of the process occurs in the liver but it is not clear that the reduction of progesterone to pregnanediol takes place in that organ.

3. Urinary pregnanediol appears to be a quantitative reflection of the amount of progesterone present but is unrelated to the degree of physiologic response.

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URINARY DEHYDROEPIANDROSTERONE IN IDIOPATHIC HIRSUTISM: INFLUENCE OF CORTISONE THERAPY*

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IN 1937 Kenyon and colleagues were unable to demonstrate a definite increase of biologically measurable urinary androgens in cases of idiopathic hirsutism (1). The following year Callow (2) observed that several women with this condition excreted moderately elevated quantities of urinary 17-ketosteroids (25–30 mg. per day), a finding since confirmed by other workers (3–5). Callow performed serial analyses on the urine of a hirsute woman with regular menses and found a variation between 16 and 26 mg. per day of 17-ketosteroids (6). When Salter and colleagues carried out digitonin alpha-beta fractionations of the urinary 17-ketosteroids of patients with this condition, 2 out of 7 patients showed slightly elevated beta fractions (7). The quantitative variation in urinary total 17-ketosteroid excretion in hirsute women was not understood to be systematic until Koets studied several such patients throughout their menstrual cycle (8) and observed a cyclic increase of urinary 17-ketosteroid excretion which appeared to occur at the time of ovulation. On the other hand, no consistent variation has been detected in the urinary excretion of 17-ketosteroids by normal women during the menstrual cycle (8–13). Merivale found that the cyclic increases in urinary 17-ketosteroid excretion of abnormally hirsute women corresponded to the peaks of pregnanediol excretion (14). He also noted that these peaks of excretion were absent in a hirsute woman who did not ovulate. In normal women pregnanediol has been shown to be excreted in maximal amount during the luteal phase (15–16).

Recently, it has been discovered by Jones, Howard and Langford that

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cortisone therapy may be associated with a diminution of urinary 17-ketosteroid excretion in certain women with idiopathic hirsutism (17). In the present study, the urinary excretion of dehydroepiandrosterone-like compounds (DHIA steroids) and 17-ketosteroids was measured in women with idiopathic hirsutism before and during cortisone therapy. Control studies with cortisone were also made on 2 normal women.

METHODS

All determinations were made on 24-hour urine collections which had been preserved with 15 ml. of 25 per cent acetic acid. Hydrolysis with 10 per cent hydrochloric acid and extraction with carbon tetrachloride were carried out as previously described (19). The Zimmermann reaction was performed on neutral extracts which had not been treated with Girard's reagent. The final Zimmermann color was read in a Klett-Summerson photoelectric colorimeter without the use of a color correction factor. Quantitative measurements of DHIA steroids and the spectrophotometric curves of the DHIA reaction were made as described elsewhere (18–20). The values of 0.2 to 0.8 mg. of urinary DHIA steroids per day which were obtained in normal adults agree with the values for the recovery of dehydroepiandrosterone from adult urine by Callow and Callow (21) and the alpha-beta fractionations of adult urine by Frame (22). However, studies of the effect of hydrochloric-acid hydrolysis have revealed that a considerable part of the dehydroepiandrosterone of urine is destroyed by this procedure (23). Bitman and Cohen have recently found that acetate-buffer hydrolysis resulted in a yield of dehydroepiandrosterone as high as 8 per cent of the total 17-ketosteroid excretion (24). For these reasons the data on DHIA steroid excretion reported here should be interpreted to represent relative rather than absolute urinary excretion values for dehydroepiandrosterone.

Relatively water-soluble reducing corticoids ("11-oxysteroids") of urine were determined by the phosphomolybdic-acid color reaction on chloroform extracts (25) which had been subjected to benzene-water partition but not treated with Girard's reagent.

RESULTS

Control studies in normal adults

Table 1 gives values for the excretion of DHIA steroids by normal adult subjects. Figure 1 demonstrates the lack of effect on urinary 17-ketosteroids of 75 mg. per day of cortisone acetate administered orally to 2 normal women over a period of ten days. In both subjects there was an increase of urinary reducing corticoids during cortisone therapy. Table 1 also shows

TABLE 1. COMPARISON OF URINARY 17-KETOSTEROID AND DHIA STEROID EXCRETION IN NORMAL ADULTS AND IN ADULT FEMALES WITH IDIOPATHIC HIRSUTISM

Data are given on 1 normal man, 2 normal women and 4 women with idiopathic hirsutism who were treated with cortisone acetate.

Subject	Sex	Age (yrs.)	Therapy (mg./day)	17-Ketosteroids		DHIA steroids		Urine volume		Urine aliquot for DHIA reaction		17-KS aliquot for DHIA reaction		J.H. Hosp.No	Remarks
				Control	During therapy	Control	During therapy	Control	During therapy	Control	During therapy	Control	During therapy		
				mg./24 hrs.	mg./24 hrs.	mg./24 hrs.	mg./24 hrs.	ml./24 hrs.	ml./24 hrs.	ml.	ml.	μgm.	μgm.		
Normal Adults															
C.M.	M	28	Cortisone, 75 p.o.	13.1	12.1	0.3	0.3	750	750	20	20	350	322	—	Normal adult
L.G.	M	33	None	16.3	—	0.4	—	1670	—	10	—	98	—	—	Normal adult
C.R.	F	26	None	4.4	—	0.4	—	750	—	10	—	58	—	—	Normal adult
M.L.G.	F	34	Cortisone, 75 p.o.	3.2	3.71	0.2	<0.2	1230	—	10	—	40	—	—	Normal adult
M.E.C.	F	23	Cortisone, 75 p.o.	8.4	7.9	0.3	0.8	1300	—	10	—	89	—	—	Normal adult
Adult females with idiopathic hirsutism															
O.B.	F	21	Cortisone, 100 p.o.	12.2	8.5	1.4	0.3	680	2750	10	50	180	154	569929	Hirsutism, amenorrhea
C.S.	F	26	Cortisone, 50 p.o.	21.8	9.6	1.7	0.5	830	1270	10	10	75	75	532215	Hirsutism, sterility
E.W.	F	40	Cortisone, 50 i.m.	10.6	2.0	1.1	0.5	1470	2500	20	20	144	20	220586	Hirsutism, amenorrhea
L.M.	F	19	Cortisone, 50 p.o.	35.1	8.1	2.8	0.0	2880	1950	10	10	122	41	539831	Hirsutism, infrequent periods
L.H.	F	26	None	23.5	—	3.7	—	1300	—	10	—	180	—	381172	Hirsutism, habitual abortion
B.L.	F	18	None	10.3	—	1.6	—	850	—	10	—	120	—	A88488	Hirsutism, normal periods
E.E.	F	20	None	19.6	—	4.2	—	1360	—	10	—		—	603439	Hirsutism

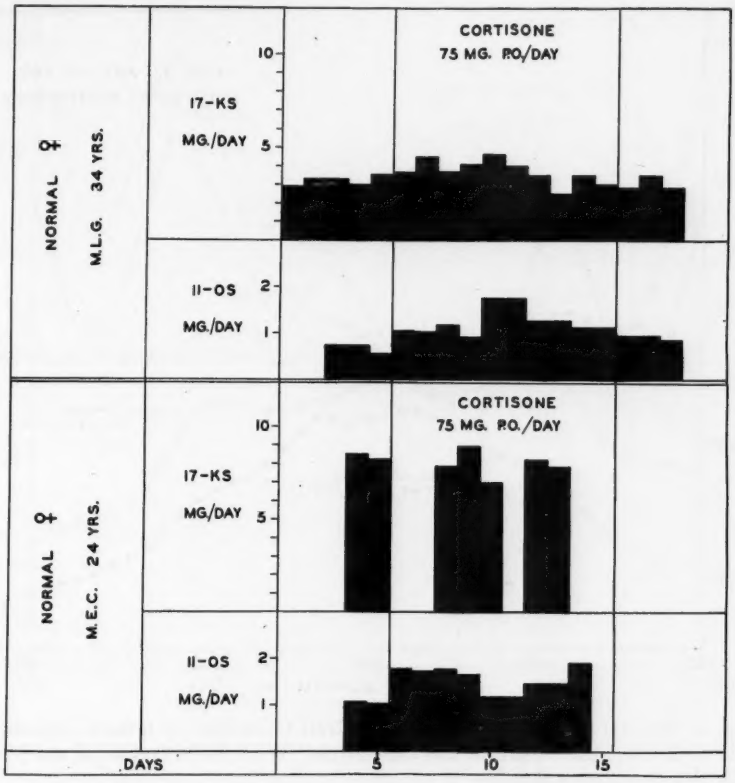

FIG. 1. Effect of cortisone acetate therapy on urinary 17-ketosteroid and reducing corticoid excretion in 2 normal women.

the lack of effect of cortisone in this dosage on the urinary 17-ketosteroids of an adult male (Subject C.M.).

Studies in women with idiopathic hirsutism

Table 1 provides data on urinary 17-ketosteroids and DHIA steroids of 7 women with idiopathic hirsutism. Four of these patients received cortisone acetate, and their urinary 17-ketosteroids and DHIA steroids were also measured during treatment. Three of these women excreted 17-ketosteroids in the normal range (10.3–12.2 mg. per day), and 4 showed an abnormally elevated excretion of 17-ketosteroids (19.6–35.1 mg. per day). All 7 women excreted excess amounts of DHIA steroids (1.1–4.2 mg. per day) in comparison with the 5 adult controls.

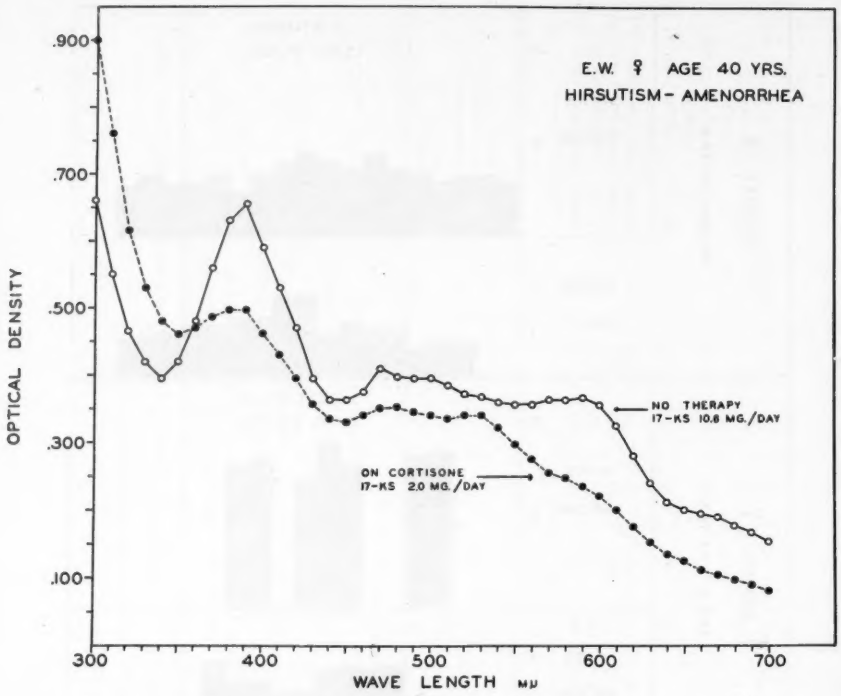

FIG. 2. Spectral absorption curves of the DHIA reaction on urinary steroids in a woman with idiopathic hirsutism and amenorrhea. There is diminution of the peak at 600 mμ. during cortisone therapy.

The 4 women with idiopathic hirsutism who were treated with cortisone acetate showed a diminution of urinary 17-ketosteroid and DHIA steroid excretion to values such as were found in the normal individuals.

Figures 2 and 3 show spectrophotometric curves of the DHIA reaction obtained on urinary steroids of Patients E. W. and O. B. These figures demonstrate the small absorption peak at 600 mμ, which almost completely disappeared when the patients were treated with cortisone. The change in configuration of these spectral curves during cortisone therapy is reminiscent of the change previously recorded in the urinary steroids of a very hirsute girl with congenital adrenal hyperplasia and pseudohermaphrodism who was treated with cortisone (19).

DISCUSSION

The data which have been presented indicate that cortisone therapy did not significantly affect the urinary excretion of 17-ketosteroids in the 2

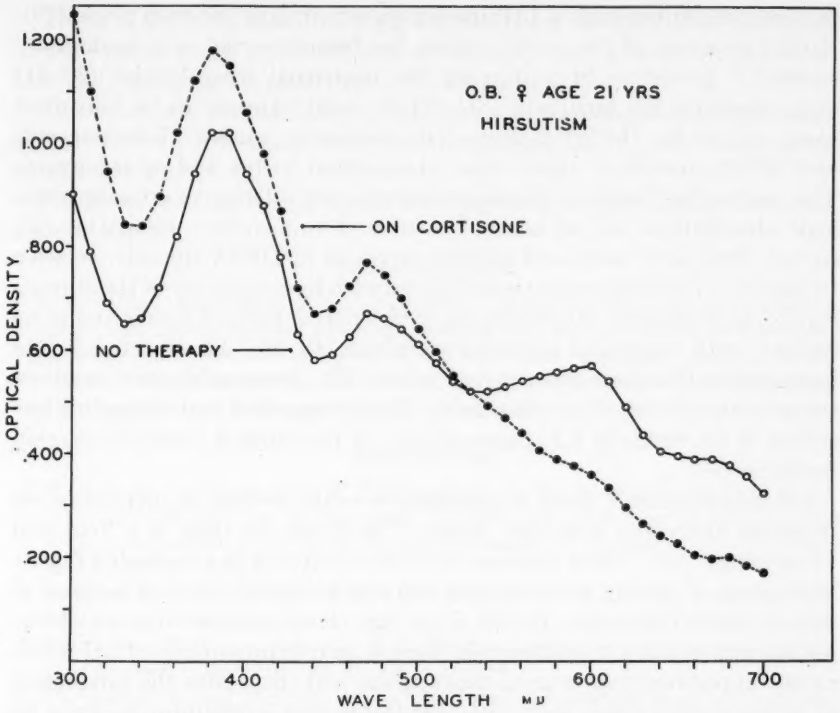

FIG. 3. Spectral absorption curves of the DHIA reaction on urinary steroids in a woman with idiopathic hirsutism. The change in configuration of the curve during cortisone acetate therapy is similar to that seen in Figure 2.

normal women who were studied. Due to the small quantities of DHIA steroid involved, it was not possible to be sure whether or not cortisone affected DHIA steroid excretion in the normal women. On the other hand, cortisone therapy was associated with a definite diminution in urinary excretion of both 17-ketosteroids and DHIA steroids in the women with idiopathic hirsutism who were observed. This observation is similar to those which have been made in cortisone-treated patients with congenital adrenal hyperplasia (19, 26, 27). In the latter disease state there is increasing evidence that cortisone suppresses excess production of endogenous ACTH.

In 1935 Stein and Leventhal described a series of patients with polycystic ovaries, half of whom were abnormally hirsute (28). It has been hypothesized that such patients suffer from pituitary overactivity, and that the hormone being produced in excess is luteinizing hormone (LH), although

no direct measurements of LH urinary excretion have yet been made (29). Partial resection of the cystic ovaries has been reported as a moderately successful procedure in improving the menstrual irregularities (29–31) and correcting the hirsutism (31). There would appear to be two most likely origins for the precursors of the excessive urinary 17-ketosteroids and DHIA steroids in these cases: the adrenal cortex and/or the ovary. This author has found no published information relative to gross or histologic observations on the adrenal cortices of women with idiopathic hirsutism. Ordinarily increased urinary excretion of DHIA steroids (relative to the other 17-ketosteroids) is associated with hyperactivity of the adrenal cortex, as in patients with virilizing or hirsutizing adrenal tumor and some patients with congenital adrenal hyperplasia (19, 20). This fraction is also increased in the urine of castrated males (32), presumably as a result of compensatory adrenocortical activity. Koets suggested that idiopathic hirsutism is the result of a hypersensitivity of the adrenal cortex to ovarian hormone (8).

On the other hand, there is considerable evidence that the normal ovary produces androgen, a subject recently reviewed by Huis in't Veld and Dingemanse (33). These authors have demonstrated in a castrated female diminution of urinary androsterone and etiocholanolone and an increase of dehydroepiandrosterone. Hence, Plate has theorized that in cases of hirsutism with ovarian hyperthecosis, there is an overproduction of LH which causes hypertrophy of ovarian theca tissue and stimulates the production of testosterone by the ovary (30). McArthur and Zygmuntowicz have recently made a chromatographic separation of the urinary 17-ketosteroids in a woman with ovarian hyperthecosis (34). Although the total daily 17-ketosteroid excretion was normal, there was a grossly abnormal chromatographic pattern.

As yet no adequate data seem to be available to indicate whether it is adrenal cortex or ovary that is hyperfunctioning in patients with idiopathic hirsutism. Improved techniques for the estimation of pituitary tropic hormones such as LH, may provide the answer to this question (35).

SUMMARY

The urinary excretion of 17-ketosteroids and dehydroepiandrosterone-like steroids (DHIA steroids) was studied in 2 normal women and in 7 women with idiopathic hirsutism.

Urinary steroid studies during cortisone acetate therapy were also made in the 2 normal women and in 4 of the women with idiopathic hirsutism.

Cortisone acetate was essentially ineffective in modifying the 17-ketosteroid excretion of the 2 normal women, when given over a ten-day period.

Three of the women with idiopathic hirsutism excreted 17-ketosteroids in the normal range and 4 showed abnormally high 17-ketosteroid excretion. All 7 patients excreted excess DHIA steroids.

The 4 patients with idiopathic hirsutism who were treated with cortisone acetate showed a decrease of 17-ketosteroid and DHIA steroid excretions to normal values.

Problems relating to the possible endogenous source of such hormones are discussed.

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URINARY STEROID EXCRETION AFTER TOTAL ADRENALECTOMY. I. LEVELS OF 17-KETOSTEROIDS IN CANCER PATIENTS MAINTAINED ON VARYING AMOUNTS OF CORTISONE ACETATE AND GLYCYRRHIZIN*

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PROMPTED by the reports of Groen (1, 2) concerning successful use of glycyrrhizinic acid for maintenance of a patient suffering from Addison's disease, we have recently investigated the feasibility of using the same compound as replacement medication in cases of total bilateral adrenalectomy. Glycyrrhizin is, from the standpoint of structural formulae, but distantly related to the adrenocortical steroids. Nevertheless, it has been shown (3) to influence many of those metabolic phenomena previously considered to be under the control of the adrenal cortex.

Therefore, it has seemed reasonable to investigate the possible *in vivo* conversion of glycyrrhizin to biologically active steroids. For this purpose, patients maintained on decreasing daily dosages of cortisone acetate have been studied.

MATERIALS AND METHODS

Two females with advanced disseminated carcinoma of the breast and 1 male with metastatic prostatic carcinoma were utilized for this study. Both of the females were postmenopausal, and the male had previously been castrated. In each instance the patient was subjected to a bilateral total adrenalectomy, designed to alleviate distressing symptoms which could not be controlled by more conservative measures.

Each patient was maintained satisfactorily after adrenalectomy on 25

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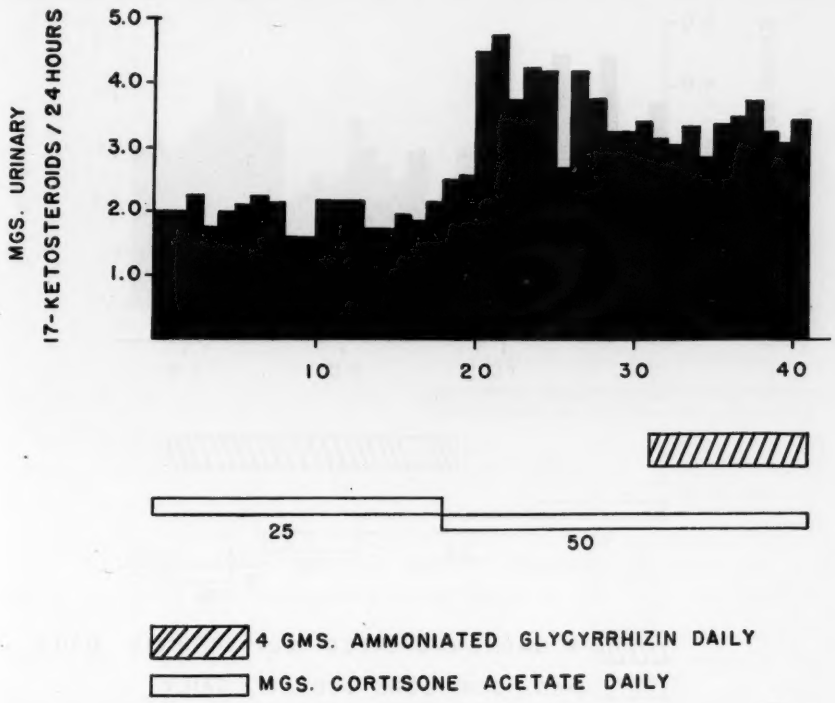

FIGURE 1

mg. of cortisone acetate orally, given in two equally divided daily doses. Later, 4 grams of ammoniated glycyrrhizin (U.S.P.) was added to the 25-mg. maintenance dose of cortisone acetate. Both compounds were administered orally during this portion of the study. Gradually, the daily dosage of cortisone was decreased to zero but the dosage level of glycyrrhizin remained constant.

Throughout the study, all of the urine excreted by each patient was collected as 24-hour samples. These samples were refrigerated for periods not exceeding forty-eight hours prior to hot acid hydrolysis and continuous ether extraction for twenty-four hours (4). The ether extracts were treated according to methods previously described (5). Determinations of 17-ketosteroid content were made on the total neutral fraction by the Zimmermann reaction (6). In each assay a urine blank was utilized for colorimetry in order to preclude error contributed by nonsteroidal chromogenic substances.

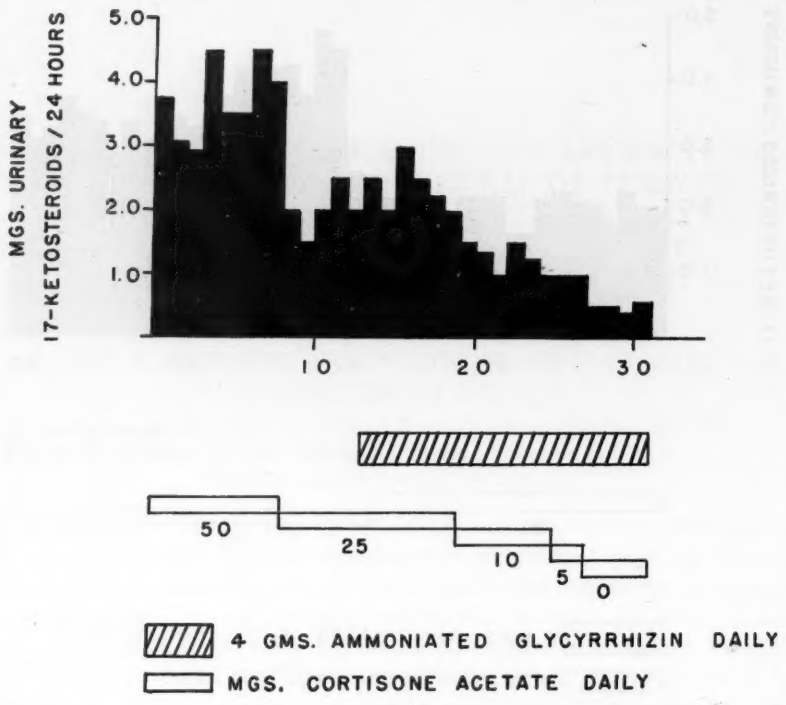

FIGURE 2

RESULTS

Case No. 1, F. L. (Fr. Del. Hosp. No. 1019)

Diagnosis: metastatic adenocarcinoma of the breast and post-radiation-induced menopause.

Throughout a 19-day collection period after bilateral adrenalectomy this patient was found to have a mean daily urinary 17-ketosteroid excretion of 1.99 mg. The maintenance dose of cortisone acetate was 25 mg. daily. Increase in the administered cortisone to 50 mg. daily yielded a concomitant rise in the urinary 17-ketosteroids to a mean level of 3.6 mg. per twenty-four hours. The addition of glycyrrhizin to the regimen of oral medication did not result in any palpable change in the excretion of 17-ketosteroids in the urine (Fig. 1).

Case No. 2, J. S. (Fr. Del. Hosp. No. 1744)

Diagnosis: metastatic adenocarcinoma of the prostate and post-bilateral orchiectomy.

During five days' maintenance on 25 mg. of cortisone acetate daily in the post-adrenalectomy period the mean level of 17-ketosteroids in the urine was 2.0 mg. per twenty-four hours. The addition of 4 grams of ammoniated glycyrrhizin to the regimen did not produce a significant change in the amount of urinary 17-ketosteroids. Gradual diminu-

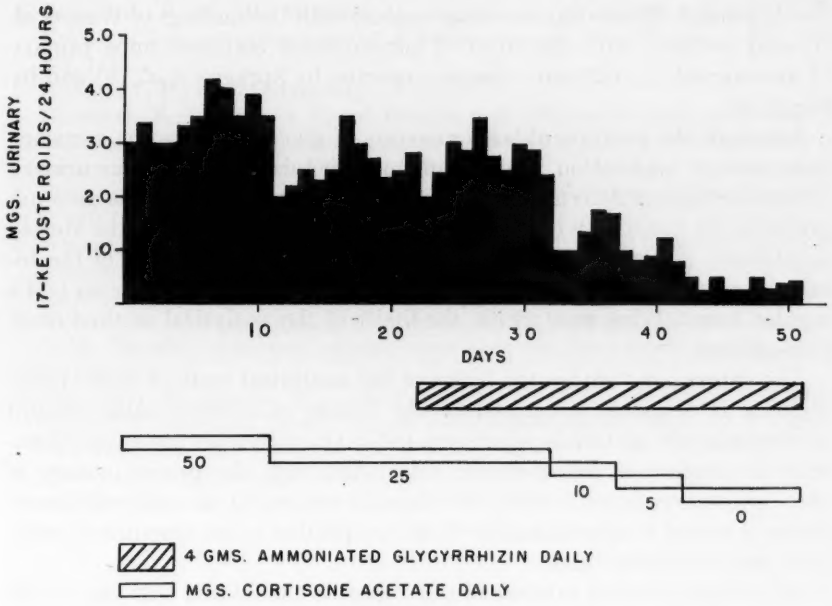

FIGURE 3

tion of the cortisone dosage with an unaltered glycyrrhizin intake (4 Gm. daily) was accompanied by a progressive decrease in amounts of 17-ketosteroids excreted. Complete withdrawal of cortisone and reliance upon glycyrrhizin maintenance resulted in urinary 17-ketosteroid levels which were too low for accurate determination by the technique employed (Fig. 2).

Case No. 3., R. S. (Fr. Del. Hosp. No. 1709)

Diagnosis: metastatic adenocarcinoma of the breast and post-radiation-induced menopause.

A maintenance dose of 50 mg. of cortisone acetate daily for this patient yielded a mean urinary 17-ketosteroid level of 3.5 mg. per twenty-four hours throughout a ten-day trial period after bilateral adrenalectomy. Reduction from 50 mg. to 25 mg. in the cortisone dosage produced a mean daily excretion of 2.5 mg. of 17-ketosteroids. The addition of 4 grams of glycyrrhizin to the daily cortisone dosage (25 mg.) resulted in an essentially unaltered 17-ketosteroid level (2.7 mg. per twenty-four hours). Progressive reduction to 10, 5, and 0 mg. of cortisone administered daily was accompanied by mean daily excretion levels of 1.3, 0.94 and 0.41 mg., respectively (Fig. 3).

DISCUSSION

The daily excretion of urinary 17-ketosteroids in the post-adrenalectomy state parallelled the oral dosage level of cortisone acetate in Cases

No. 1, 2 and 3. These data are in agreement with the findings of West *et al.* (7) and correlate with the effect of administered cortisone upon urinary 17-ketosteroids in Addison's disease, reported by Sprague *et al.* (8) and by Engel (9).

Although the addition of large amounts of glycyrrhizin to the cortisone maintenance medication resulted in no detectable alteration in urinary 17-ketosteroids as determined by the Zimmermann reaction, this does not preclude the possibility of *in vivo* conversion of glycyrrhizin to the steroid substances. However, the 17-ketosteroid excretion in the urine of the totally adrenalectomized patients maintained entirely by glycyrrhizin and a regular hospital diet was, within the limits of the analytical method used, non-existent.

The expression "within the limits of the analytical method used" is not a cliché. It is instead prompted by the finding of a considerable amount of chromogenic materials which reacted atypically with metadinitrobenzene to produce a yellow-brown color. Although the precise nature of these substances is not known, the amounts present in the assayed urinary extracts varied in approximately direct proportion to the amounts of cortisone acetate administered.

Of perhaps greatest interest in this report is the finding that the totally adrenalectomized patient maintained exclusively upon glycyrrhizin presents an opportunity for studies on steroid metabolism hitherto not available.

SUMMARY

1. Administration of glycyrrhizin to patients maintained on oral cortisone acetate did not result in an increase in 17-ketosteroid excretion.

2. Alteration in 17-ketosteroid excretion with variation of the dosage of administered cortisone is in agreement with the data of other investigators.

3. Excretion of 17-ketosteroids by 2 patients maintained solely on glycyrrhizin was negligible.

4. That the chromogens present in the urinary extracts of cortisone-maintained patients were steroids other than 17-ketosteroids, seems indicated by the atypical yellow-brown reaction of these extracts with metadinitrobenzene.

5. Adrenalectomized patients maintained on glycyrrhizin exclusively present a unique opportunity to study steroid metabolism.

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ELECTROENCEPHALOGRAPHIC OBSERVATIONS ON PATIENTS UNDERGOING CORTISONE AND ACTH THERAPY

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THE influence of adrenocorticotropin and of cortisone on the brain-wave pattern has been casually considered in many studies which have dealt with the clinical aspects and influence of these substances on various diseases for which they have been tried.

In 1947 Grenell and McCrawley (1) reported an "increase in amplitude and some change in frequency of brain waves" after administration of adrenocortical extract to experimental animals and humans. Boland and Headley (2) elicited an increase in alpha frequency following cortisone administration.

In 1949 Thorn (3) reported a decrease of slow activity and an increase of fast activity along with the general improvement of the electroencephalogram patterns when compound E was given to patients with Addison's disease.

There are, however, very few detailed reports with serial electroencephalograms which deal with the effects of these hormones on the brain-wave patterns, and the workers on the subject have come to different conclusions.

In 1950 Hoefer and Glaser (4) examined systematically the electroencephalograms of 15 patients under ACTH therapy. They reported slow-wave abnormalities in 13 of the 15 patients, with occasional appearance of paroxysmal activity. They concluded from their observations that ACTH and cortisone have a profound influence on the excitability of the cerebral cortex.

On the other hand, Pine, Engel and Schwarz (5) who reported more recently on the electroencephalograms of 37 patients under ACTH treatment, demonstrated that 28 did not show slowing or other defects, and that 7 of 12 initially abnormal records improved while the patients under-

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went ACTH treatment. They also noted either improvement of the electroencephalogram patterns or no changes in patients who received combined ACTH and cortisone therapy.

This report is in line with a paper by Friedlander and Rottger (6) which appeared at the same time and dealt with a series of 16 patients who received cortisone. These workers also came to the conclusion that cortisone produced a tendency to normalization of the brain-wave pattern and often an increase of alpha activity.

CLINICAL MATERIAL

Our studies concern 43 patients hospitalized at the Bronx V.A. Hospital in 1950 and 1951, who were treated with ACTH or cortisone or both. None of these patients was afflicted with, or had a history of psychiatric illness. They were all referred to us from the Medical, Dermatological, Neurological and Ophthalmological Services. Thirty-two patients received only cortisone; 6, only ACTH; and 5, combined ACTH and cortisone treatment.

The distribution of diseases was as follows:

Rheumatic diseases	11 patients
Hodgkin's disease	4
Scleroderma	2
Pemphigus	2
Chronic dermatitis, not responding to other forms of treatment	5
Disseminated lupus erythematosus	2
Severe asthma	2
Pulmonary granulomatosis	1
Boeck's sarcoid	1
Kaposi's hemorrhagic sarcoma	1
A degenerative encephalopathy with encephalomalacia	1
Amyotrophic lateral sclerosis	1
Myasthenia gravis	2
Myotonia atrophica	1
Eye diseases (retinopathy, glaucoma, uveitis, etc.)	7

The clinical results of the treatment on the various diseases for which the hormones were administered is not the subject of this paper. Suffice it to say that we agree with Hoefer and Glaser as well as with Pine, Engel and Schwarz that clinical effects and electroencephalographic changes resulting from these hormones do not seem to be related.

Four patients died shortly after termination of the hormone treatment. However, all had been critically ill when this therapy was instituted. Three of these patients had suffered from advanced Hodgkin's disease and 1 from disseminated lupus erythematosus. None of the patients in our series is being currently treated with either cortisone or ACTH at our hospital and most of them have at least temporarily been discharged.

COMPLICATIONS

In 3 patients psychoses developed during, or shortly after treatment—manifested by paranoid ideation, visual and auditory hallucinations and variable mood. Orientation was intact except in 1 case. Four patients had convulsive seizures, and 1 had tetanic phenomena in the course of, and after completion of hormone therapy. Reactive depression was also observed in some cases. Several patients had various degrees of water retention and 1 exhibited signs of Cushing's syndrome. In 1 instance there was an acute exacerbation of gout three days after cortisone therapy was initiated, and treatment had to be withdrawn. There were also several instances of intercurrent acute infections (Table 1). Almost all patients who responded favorably to treatment showed some elevation in mood.

ELECTROENCEPHALOGRAPHIC STUDIES

One hundred and seventy-six recordings were obtained on the 43 patients. The tracings were made on a 6- or 8-channel Grass encephalograph. Recordings were obtained with scalp-to-ear reference, or double scalp electrode placements. In many instances, tracings were also obtained from basal structures with pharyngeal leads. All patients were hyperventilated for three minutes.

Only 2 patients had no pretreatment electroencephalograms. Of these patients, one had previously received cortisone elsewhere for fourteen months; the second came under our observation during a psychotic episode which occurred concomitantly with ACTH therapy.

Forty-one patients were tested one or two days prior to institution of treatment with cortisone or ACTH and were followed up regularly with serial electroencephalograms for the duration of their treatment. Those patients who had markedly abnormal electroencephalograms or whose records showed considerable differences at the end of their treatment period in comparison to their pretreatment records, were followed up carefully at two-week to four-week intervals—some for as long as six months after completion of therapy and after their discharge from the hospital.

RESULTS

Of the pretreatment electroencephalograms, 11 were normal, 1 doubtful, 4 borderline, 9 mildly abnormal, 9 moderately abnormal, and 7 grossly abnormal.

Fourteen moderately or grossly pathologic records seen prior to treatment became worse during treatment. Ten mildly or moderately abnormal electroencephalograms did not show any appreciable changes. Only 2 of the initially pathologic electroencephalograms showed some improvement

TABLE 1

Name, age, sex	Clinical diagnosis	Cortisone		ACTH		Complications	No. of EEG's	Electro-encephalograms			
		Length of treatment	Total amount	Length of treatment	Total amount			Pretreatment EEG	Follow-up during treatment	Follow-up post-treatment	Results of treatment
W.O'H. 33 M	Rheumat. carditis	28 days	2.5 Gm.	—	—	Influenza	6	Pathologic ampl. asym., parox. act. lft. hemisph.	Increasing dysrhyth.	Abnormal: non-focal parox., max. lft. hemisph.	Worse
HM 44 F	Rheumat. fever & carditis	29 days	2.9 Gm.	—	—	Mild depression	3	Doubtful: slow ?drowsy.	Gen. slow, 4–6 /sec., bilateral	Unchanged, slow	Unchanged
G.O. 36 M	Rheumat. arth. & psoriasis.	53 days	3.1 Gm.	—	—	Mild elation	5	Borderline: min. parox. trends	Low grade dysrhyth.	Borderline: protracted hypervent.	Slightly more abnormal
O.S. 35 M	Rheumat. arth.	6 mo. intermitt.	18.6 Gm.	—	—	"Moon face" & acne.	7	Normal: alpha record	Borderline: mild parox. trends.	Normal	Minimal change
A.D. 36 M	Gout	3 days	600 mg.	—	—	Acute exacerb. of gout	4	Mildly abnormal: non-focal, parox.	Mildly abnormal: non-focal, parox.	Unchanged	Unchanged
C.J. 63 M	Rheumat. arth.	—	—	10 days	800 mg.	Elation	3	Pathologic: focal, parox; 4–7/sec. L.C-T	More pathologic: L.T-C	Pathologic: like pretreat. pattern	Worse
J.D. 33 M	Rheumat. arth.	2 courses prior to adm. Poor resp. 10 days	1.2 Gm.	6 mo. (intermitt.)	3.8 Gm.	Hematuria; H_2O retent.	3	Borderline: min. slow, rt. hemisph.	Mildly abnormal: slow, with parox. trends	Unchanged	Little change
S.K. 32 M	Rheumat. arth.	30 days	3 Gm.	—	—	Psychosis; seizures	7	Pathologic: parox., non-focal; gen. dysrhyth.	Grossly pathologic: seizure rec. gen. cort. disorg.	Improved by anti-convulsive therapy	Worse
E.T. 38 M	Rheumat. arth.	63 days	6.7 Gm.	12 days	240 mg.	None	6	Abnormal: slow, max. post.	More dysrhythmic; max. post., rt. more.	Abnormal: slow, non-focal	Worse

TABLE 1—(*continued*)

Name, age, sex	Clinical diagnosis	Cortisone		ACTH		Complications	No. of EEG's	Electro-encephalograms			
		Length of treatment	Total amount	Length of treatment	Total amount			Pretreatment EEG	Follow-up during treatment	Follow-up post-treatment	Results of treatment
N.S. 51 M	Rheumat. arth.	65 days	5.3 Gm.	—	—	Mild euphoria.	7	Somewhat fast; ?sed. effect	Borderline: sl. dysrhyth.	Return to normal in 5 wks.	Minimal change
H.S. 36 F	Lupus erythem. & arth.	14 mo. prior to adm. & during hosp. here	100 mg. /day	(intermitt.)		Series of gen. convuls. & pleurisy	2	None	Mildly abnormal; non-focal slow	Gen. slow. while on anticonvulsants	—
P.A. 27 M	Lupus erythmatosis	3 series between Sept. & Dec.	6.1 Gm.	2 series, (intermitt.)	1.75 Gm.	Psychosis; seizures.	3	Pathologic: slow, parox., max. C	Gen. slow, more parox. dur. hypervent.	Unchanged	Unchanged
G.V. 40 M	Hodgkin's dis.	19 days	2 Gm.	—	—	Cushing's syndrome; hepatitis.	5	Mildly abnormal: parox. trends	Mildly abnormal: low grade dysrhyth. C-O	Gradual improv. to borderline in 3 mo.	Slightly more abnormal
W.L. 25 M	Hodgkin's dis.	13 days	2.3 Gm.	—	—	Elation; diarrhea	6	Abnormal: non-focal, parox.	More grossly pathologic	Abnormal: returning to pre-treat. patterns	Worse
E.N. 35 M	Hodgkin's dis.	4½ mo. intermitt.	9.3 Gm.	—	—	One convuls. episode	2	Mildly abnormal: slow, no seiz., discharges	Gen. faster than pre-treatment	Died	Slightly faster
D.D. 25 M	Hodgkin's dis.	48 days	5.1 Gm.	—	—	Abscess: elation	4	Abnormal: slow, max. R. C-O	More pathologic: non-focal parox.	Borderline	Worse
M.A. 36 M	Kaposi's hemorr. sarcoma.	27 days	4.6 Gm.	—	—	None	4	Abnormal: marked cerebral dysrhyth.	Abnormal: non-focal parox., max. L. C-P.t.	Returning to pretreat. pattern	Somewhat worse
F.B. 27 M	Boeck's sarcoid	3½ mo.	7.4 Gm.	—	—	Euphoria; H_2O retent.	7	Borderline: min. slow, F-C area	Borderline: becoming mildly abnormal	Mildly abnormal: slow, sl. dysrhyth.	Slightly worse
F.S.S. 23 M	Pulm. granulomatosis & fibrosis	15 days	5 Gm.	—	—	Mild elation	2	Normal: alpha record.	Mildly abnormal: parox. trends, max. left.	—	Slight change

TABLE 1—(*continued*)

Name, age, sex	Clinical diagnosis	Cortisone		ACTH		Complications	No. of EEG's	Electro-encephalograms			
		Length of treatment	Total amount	Length of treatment	Total amount			Pretreatment EEG	Follow-up during treatment	Follow-up post-treatment	Results of treatment
J.R. 30 M	Asthma	16 days	1.4 Gm.	—	—	None	4	Mod. parox. posteriorly	More grossly abnormal: non-focal seizure act.	Abnormal: non-focal parox., max. posteriorly	Worse
S.S. 36 M	Asthma	14 days	1.6 Gm.	—	—	None	2	Normal	Borderline: somewhat slow, C-O	—	Little change
F.A. 36 M	Chronic pneumonitis	—	—	10 days	250 mg.	Paranoid psychosis	1	None	Essent. normal patterns dur. psychosis.	—	—
Y.T.C. 61 M	Dermat. exfoliativa	2½ mo. (intermitt.)	3.15 Gm.	—	—	None	5	Mildly abnormal: sl. dysrhyth.	Mildly abnormal: sl. dysrhyth.	Borderline	Essentially unchanged
A.K. 26 M	Bechet dis. & eryth. bullosa.	17 days (intermitt.)	2 Gm.	—	—	None	3	Mildly abnormal: slow F-C	Mildly abnormal: slow F-C	—	—
E.K. 44 M	Gen. chron. dermatitis.	6 days	700 mg.	—	—	None	2	Normal	Normal	—	Unchanged
R.G. 29 M	Gen. mycosis.	19 days	2.3 Gm.	—	—	Mild euphoria	3	Abnormal: mild parox. bilat., C-O.	Abnormal: non-focal parox., max. C-T-O	Borderline: mild. parox.	Slightly worse
J.F. 27 M	Scleroderma & rheumat. arth.	10 days	1 Gm.	—	—	None	2	Normal: low voltage	Mildly abnormal: somewhat parox.	—	Slight change
D.N. 58 M	Scleroderma	5½ mo. (intermitt.)	16 Gm.	—	—	Hematuria; edema	11	Pathologic: gen. cerebral dysrhyth.	More grossly pathologic dysrhyth.	Abnormal: return. grad. to pre-treat. pattern	Worse

TABLE 1—(*continued*)

Name, age, sex	Clinical diagnosis	Cortisone		ACTH		Complications	No. of EEG's	Electro-encephalograms			
		Length of treatment	Total amount	Length of treatment	Total amount			Pretreatment EEG	Follow-up during treatment	Follow-up post-treatment	Results of treatment
T.R.D. 32 M	Neuro-dermatitis	13 days	1.6 Gm.	—	—	None	3	Abnormal: non-focal, parox. slowing.	More grossly pathologic non-focal parox.	Abnormal: similar to pre-treat. pattern	Worse
S.G. 50 M	Pemphigus	6 mo. (intermitt.)	18.4 Gm.	—	—	Euphoria; rounding of face	9	Pathologic: slow wave, & spike seizure activity, bilat.	Improving, tho' remain. dysrhythmic	Reverting to pre-cortisone pattern	Slightly improved
J.S. 37 M	Pemphigus	3½ mo.	12.5 Gm.	34 days	1.23 Gm.	Edema	6	Abnormal: non-focal, slow, more on left.	Abnormal: no essential change	—	No change
R.H. 51 M	Amyotrophic lat. sclerosis	29 days	3 Gm.	—	—	Mild euphoria	4	Mildly abnormal: parox. trends, rt. hemisph.	Mildly abnormal, or borderline	Min. slowing	No change
J.M. 32 M	Myotonia atrophica	—	—	10 days	1 Gm.	None	2	Mildly abnormal: amplit. asym., mild slowing.	Mildly abnormal: flat. rt. hemisph., gen. slow.	—	Essentially unchanged
F.C. 34 M	Encephalomalacia	2 mo. (intermitt.)	—	—	—	Tetany	9	Diffusely pathologic: stupor record	Essent. the same	—	No change
W.K. 33 M	Myasthenia gravis	—	—	5 days	0.5 Gm.	None	2	Normal	Normal	—	No change
A.L. 32 M	Myasthenia gravis	—	—	10 days, 2 courses	1 Gm.	None	3	Normal	Normal	Normal	No change

TABLE 1—(*continued*)

Name, age, sex	Clinical diagnosis	Cortisone		ACTH		Complications	No. of EEG's	Electro-encephalograms			
		Length of treatment	Total amount	Length of treatment	Total amount			Pretreatment EEG	Follow-up during treatment	Follow-up post-treatment	Results of treatment
A.C. 32 M	Optic neuritis	30 days	3.7 Gm.	—	—	Agitated depression following treatment	3	Normal	Normal	Normal: except marked build-up dur. hypervent.	Unchanged
D.R. 31 M	Uveitis	—	—	21 days	1.7 Gm.	None	3	Abnormal: slow, max. RO-RPT	Abnormal: more dif. parox.	No change	Worse
J.P. 54 M	Symp. ophthalmitis.	21 days	2.4 Gm.	—	—	None	4	Mildly abnormal: nonspecific, slow, left.	Mildly abnormal: somewhat parox. LC-T	Borderline	No gross change
S.F. 29 M	Glaucoma	30 days	2.8 Gm.	—	—	Abscess	2	Mildly abnormal: non-focal, parox. trends.	More grossly pathologic after 4 days	—	Worse
J.P. 28 M	Retinopathy	21 days	2.3 Gm.	—	—	None	2	Normal	Normal	—	No change
J.S. 32 M	Glaucoma	3 days	400 mg.	—	—	Severe edema	2	Essent. normal, except for build-up during hypervent.	Somewhat slow, probably drowsy; mod. build-up dur. hypervent.	—	No change
H.P.H. 37 M	Cataract	24 days	2.4 Gm.	—	—	None	3	Borderline	Borderline	—	No change

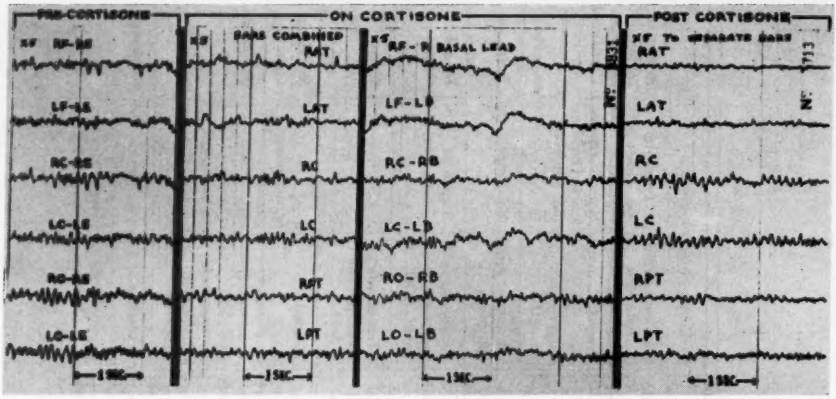

FIG. 1. *R.H.*, age 51. Clinical diagnosis: amyotrophic lateral sclerosis. *Precortisone* EEG: borderline; minimal amount of slowing; fast frequencies, not unusual for patient's age.

After twenty-one days on cortisone (total amount received at time of retesting, 2.1 Gm.), EEG: borderline, with small amount of slow activity; no significant change from pretreatment record.

One month after termination of cortisone therapy. EEG shows tracings similar to those in pretreatment record.

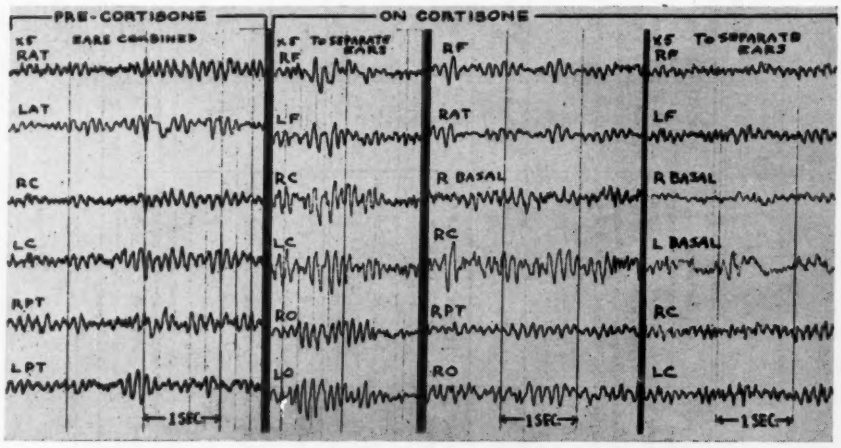

FIG. 2. *M.D.*, age 52. Clinical diagnosis: scleroderma. *Precortisone* EEG: abnormal, with evidence of cerebral dysrhythmia in the left hemisphere.

After twenty-one days on cortisone (total amount received at time of retesting, 2.4 Gm.), EEG: more grossly pathologic in both hemispheres and in basal area than prior to treatment.

(1 of a patient with Hodgkin's disease, 1 of a patient with pemphigus). Of the initially normal electroencephalograms, however, 5 remained normal, 4 became mildly abnormal and only 1 showed a development to gross abnormality. Three borderline records remained essentially unchanged; in 2 patients (1 receiving ACTH and 1 receiving cortisone) a moderate amount of fast activity developed.

The abnormal electroencephalograms included irregular, slow-wave activity of usually 3–7/sec. frequency and paroxysmal bursts, usually of a non-focal variety. In some instances the records were so abnormal that they could be considered as consistent with a convulsive disorder, and in these instances the ward physicians were notified to watch these patients closely for appearance of clinical seizures. One of these patients did have epileptiform seizures and required anticonvulsive medication. This patient and 3 others in whom convulsions were observed during or shortly after completion of treatment with cortisone and ACTH will be reported on in detail in another paper.

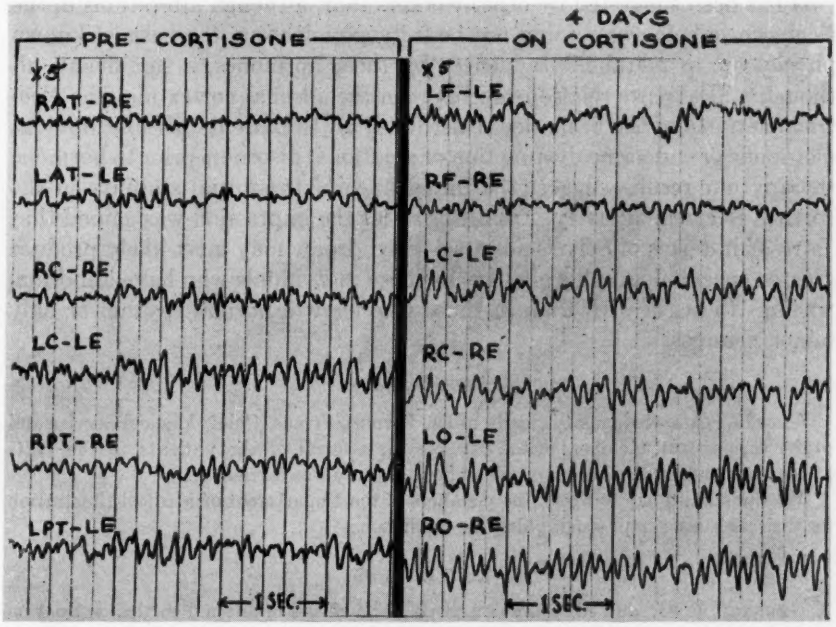

FIG. 3. *S.F.*, age 29. Clinical diagnosis: uveitis. *Precortisone* EEG: mildly paroxysmal, more so in the left hemisphere.

After four days on cortisone (total amount received at time of retesting, 800 mg.), EEG: more grossly pathologic, with bursts and small runs of non-focal paroxysmal slow activity, most marked in the left hemisphere.

CONCLUSIONS AND SUMMARY

The electroencephalographic data of 43 patients prior to, during and after completion of cortisone and ACTH therapy, or both, have been presented.

The tracings of those patients who had initially normal or borderline records remained either unchanged or showed only mild changes, with 2 exceptions. Of this group, 2 patients, 1 while receiving ACTH and 1 while receiving cortisone, showed an acceleration of rhythm.

Of the patients with moderately or grossly abnormal electroencephalograms prior to treatment, only 2 showed improvement in their brain-wave patterns while undergoing treatment. In 10 patients with mild electroencephalographic abnormalities the defects did not become more severe. However, among the moderately and severely abnormal electroencephalograms we noticed a tendency to an increase in the defect, with occasional development of patterns compatible with those seen in convulsive disorders.

It has been suggested by other workers that, although alterations in the electroencephalograms could not be fully explained on the basis of known physiologic or metabolic influences by these hormones, a significant, although still obscure relationship between the adrenal cortex and the electrical activity of the brain does exist (3, 4, 5). In patients without obvious metabolic or endocrine dysfunction or emotional disorders prior to hormone therapy our results suggest the importance of the initial stability in the cortical electrical activity. From this series the impression was gained that "stress" in terms of Selye's adaptation syndrome may most likely produce greater encephalographic changes in those individuals who have abnormal tracings to begin with than in those who show a normal rhythm or only minor changes.

Acknowledgments

Grateful acknowledgment is made to Dr. Bernard Straus, Chief, Medical Service and to the various staff members of the Services for referral of the patients to the EEG Laboratory and for their cooperation while this study was carried out.

We should also like to thank the members of the Department of Medical Illustration for their assistance in photographing the tracings.

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EFFECT OF EPINEPHRINE ON URINARY pH AND ELECTROLYTE EXCRETION IN MAN*

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INTRODUCTION

THE effect of epinephrine and nor-epinephrine on the kidney is a subject which has received considerable attention for many years. Earlier, most interest was focused on the effect of these hormones on the vascular bed. More recently, studies of the electrolyte changes have appeared (1–4).

It has been found that epinephrine and nor-epinephrine will cause a significant increase in the pH of the urine in rabbits (5); however, no such studies have been carried out in man.

Ureteral catheterization in our clinic has revealed that the urine coming from the kidneys almost invariably has a higher pH than that of bladder urine. In cases in which patients have had an adrenergic reaction from instrumentation, this difference in pH has been as much as 2.5 pH units.

The possible effect of epinephrine on urinary pH seems to be of more than academic interest. For instance, it has been shown that rabbits injected with hemoglobin will exhibit a physiologic increase in the pH of urine. This appears to prevent the precipitation of hemoglobin in the renal tubules. A prevention of this increase, which can be brought about by the administration of an antiadrenergic substance, may result in kidney damage (5). Miles and co-workers (6) have described an impressive water, sodium and chloride diuresis in a hypertensive subject in response to emotion.

The well known pattern of diurnal variations of urinary pH in man has never been explained satisfactorily. The so-called alkaline tide following awakening in the morning is independent of meals and production of gastric acid (7). The other alkaline tides during the day usually occur a few hours after a meal, but these are also seen in patients with achylia. If the

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adrenal medullary hormones have an alkalinizing effect on the urine of man, transitory changes in adrenergic activity may well play a role in the pattern of akaline tides.

It was the object of this study to determine whether the reaction of urine in man is affected by the administration of epinephrine. Since such an investigation would be incomplete without a study of electrolyte excretion, the urine has been analyzed for sodium, potassium, phosphate, chloride and sulfate.

METHODS

Each of 10 male medical students received one subcutaneous injection of epinephrine (Suprarenin bitartrate[1]) (0.2 cc. of 1:1000). Prior to the injection, urine samples were collected for a period of approximately twenty minutes. Fifteen minutes following the administration of epinephrine and again fifteen minutes later, two more specimens were voided and the pH determined immediately. Sodium and potassium were determined on all three urine samples.

In addition to these normal subjects, 2 patients were used in this study. A Foley catheter was placed in the bladder of each patient and the urine was allowed to flow into an apparatus which continuously recorded the pH and output (8). During a 24-hour period the urine was collected frequently and analyzed for sodium, potassium, chloride, phosphate and sulfate. The pH was also determined on these samples after exposure to air.

During the course of a 24-hour experiment both patients were given 0.4 cc. of epinephrine (1:1000) subcutaneously. Blood pressure was measured before, and at frequent intervals after the administration of epinephrine.

The first patient was a 50-year-old woman, C, who had been studied several times urologically without positive findings. Immediately prior to the present study her blood chemical findings, sedimentation rate and hematologic data were normal. Results of a phenolsulfonphthalein kidney function test were normal, and an intravenous pyelogram showed no diagnostic findings. Her blood pressure fluctuated—the systolic between 150 and 160 and the diastolic between 80 and 90.

One 24-hour study was obtained on this patient. Prior to, and during the procedure she received a well balanced hospital diet, which contained approximately 10 grams of sodium chloride a day.

The second patient, H, was a 19-year-old boy who had suffered a severe cerebral concussion, a fracture of the base of the skull, and multiple facial and mandibular fractures. He was unconscious for several months and was still unconscious at the time these experiments were performed. His physical condition was good and his temperature was

[1] Supplied through the courtesy of Winthrop-Stearns, Inc.

normal. Because of difficulty with breathing, a tracheotomy had been performed. He had an indwelling catheter in his bladder, since he was unable to void spontaneously. Cord damage was suspected, probably at a cerebral level, since he had pathologic reflex changes and bilateral hand and foot drop. There was no history of kidney injury and the urine was clear on admission. His serum nonprotein nitrogen level was normal and his kidney function remained good. At the time these experiments were performed, his condition was relatively unchanged and blood chemistry gave normal results.

Three separate experiments were carried out on this patient. Prior to, and during the first two experiments he received per diem a total of 3,850 cc. of fluid through a stomach tube. This fluid contained 2,500 calories and 11.5 grams of sodium chloride. Prior to, and during the last experiment the patient received a salt-poor diet, which furnished only 30 mg. of sodium chloride for a 24-hour period. His daily intake was 1,030 calories in 3,250 cc. of fluid.

The sodium and potassium content of the urine and of the serum was determined, using a Beckman model DU spectrophotometer with a flame photometer attachment. Chlorides in the urine were determined according to the method described by Sendroy, and modified by Van Slyke and Hiller (9). Urine was analyzed for phosphate by the method of Fiske and SubbaRow (10) and for sulfate by Fiske's modification of the method described by Rosenheim and Drummond (11).

RESULTS

The effect of epinephrine on urinary pH and on water, sodium and potassium excretion in 10 male medical students is shown in Table 1. An increase in pH was seen in 8 of the 10 subjects. Seven of the 10 exhibited an increase in water excretion. The changes in electrolyte excretion were inconsistent. Most of the students responded to the administration of the epinephrine with an increase in systolic blood pressure of approximately 20 mm. of Hg. No correlation was found between their blood pressure response and urinary excretion. In order to see if the lack of reproducibility was a result of the experimental conditions, the effect of epinephrine on 2 catheterized patients was investigated. This permitted a more frequent collection of urine samples.

Figure 1 shows the urinary pH as observed with the continuously recording pH meter.

It may be seen from Table 2 that the subcutaneous administration of 0.4 cc. of epinephrine (1:1000) caused a pronounced increase in all the electrolytes which were determined, as well as in pH. These increases occurred before an increase in water excretion was evident.

Identical experiments were performed on Patient H and similar results obtained. The first of these is presented in Table 3A and the pH recording is shown in Figure 1 (Patient H-1); the pH recording from the second experiment is depicted in Figure 1 (H-2).

TABLE 1. EFFECT OF EPINEPHRINE ON URINARY pH AND ON WATER, SODIUM AND POTASSIUM EXCRETION IN 10 NORMAL SUBJECTS

Subject No.	Mins. after epinephrine	Water excretion (cc/min.)	pH of urine	Urinary Na^+ (μEq./min.)	Urinary K^+ (μEq./min.)
1	0*	0.67	5.58	241.3	72.9
	19	0.61	5.73	215.5	65.4
2	0	0.54	5.50	79.8	33.2
	21	0.52	6.20	83.6	22.7
	33	0.73	5.85	113.0	27.4
3	0	0.44	5.7	57.0	52.7
	20	0.02	5.86		
	35	1.00	5.72	157.8	114.0
4	0	1.45	5.4	299.9	92.2
	15	1.35	5.8	263.0	93.9
	30	1.66	5.5	292.5	52.7
5	0	4.54	5.9	164.9	87.7
	18	7.40	6.4	72.5	71.0
	34	8.43	6.49	104.5	108.1
6	0	0.82	5.4	107.2	124.4
	16	0.95	5.32	103.8	132.6
	32	1.94	5.10	136.6	147.2
7	0	0.55	6.20	57.1	58.3
	20	0.46	6.00	26.7	41.3
	38	0.50	5.90	33.5	27.0
8	0	0.52	5.7	145.5	38.3
	17	0.66	6.2	109.7	34.9
	32	0.66	6.2	167.7	24.9
9	0	0.40	4.8	64.1	35.2
	15	0.30	5.0	48.1	24.5
	30	0.23	5.3	46.3	19.3
10	0	0.91	5.1	77.4	88.2
	12	1.32	5.3	59.7	102.7
	29	5.70	5.7	105.0	110.7

* 0 indicates a twenty-minute period preceding the administration of epinephrine.

TABLE 2. EFFECT OF EPINEPHRINE ON URINARY pH AND ON WATER AND ELECTROLYTE EXCRETION IN A HOSPITALIZED PATIENT, "C," ON A NORMAL DIET

	Time (P.M.)	Urine							Blood pressure (mm. Hg)
		Na (μEq. /min).	K (μEq. /min.)	PO_4 (μMol. /min.)	SO_4 (μMol. /min.)	Cl (μEq. /min.)	Volume (cc. /min.)	pH	
Before epinephrine	12:08–1:05	103.8	61.4	4.6	31.0	159.3	3.0	5.1	180/98
After epinephrine*	1:10–1:20	185.9	140.7	36.8	36.2	241.5	2.1	6.0	200/100
	1:20–1:28	369.7	196.5	47.6	74.3	534.4	10.6	6.0	180/90
	1:28–1:39	236.2	50.8	24.3	52.0	368.5	11.8	6.0	190/94
	1:39–1:50	216.0	19.3	22.7	47.8	278.4	11.4	5.7	170/90

* A subcutaneous injection of epinephrine (0.4 cc. of 1:1000) was given at 1:10 P.M.

A

TABLE 3. EFFECT OF EPINEPHRINE ON URINARY pH AND ON WATER AND ELECTROLYTE EXCRETION IN A HOSPITALIZED PATIENT, "H-1," ON A NORMAL DIET

	Time (P.M.)	Urine							Blood pressure (mm. Hg)
		Na (μEq. /min.)	K (μEq. /min.)	PO_4 (μMol. /min.)	SO_4 (μMol. /min.)	Cl (μEq. /min.)	Volume (cc. /min.)	pH	
Before epinephrine	2:00–3:49	37.6	78.7	16.8	20.8	82.7	1.28	5.6	124/90
After epinephrine*	3:49–3:56	139.1	227.8	3.2	61.7	225.4	3.71	5.7	210/110
	3:56–4:02	317.0	174.8	18.8	70.2	324.2	8.17	6.5	180/100
	4:02–4:12	264.6	152.1	18.8	81.9	245.7	6.50	6.0	150/90
	4:12–4:20	93.2	29.2	9.8	21.4	91.9	1.80	5.9	140/90
	4:20–5:00	106.2	38.7	25.5	26.8	87.1	1.30	5.5	

* A subcutaneous injection of epinephrine (0.4 cc. of 1:1000) was given at 3:49 P.M.

B

EFFECT OF EPINEPHRINE ON URINARY pH AND ON WATER AND ELECTROLYTE EXCRETION IN A HOSPITALIZED PATIENT, "H-3," ON A LOW-SALT INTAKE

	Time (P.M.)	Urine							Blood pressure
		Na (μEq. /min.)	K (μEq. /min.)	PO_4 (μMol. /min.)	SO_4 (μMol. /min.)	Cl (μEq. /min.)	Volume (cc. /min.)	pH	
Before epinephrine	2:55–3:58	0.44	5.11	6.39	4.67	8.21	0.37	6.0	110/90
After epinephrine†	3:58–4:10	1.3	17.5	21.10	7.2	23.0	0.63	5.9	180/98
	4:10–4:23	1.6	17.5	21.10	5.8	19.5	1.23	5.9	155/92
	4:23–4:43	1.0	8.0	10.16	4.0	12.6	0.70	5.9	145/100

† A subcutaneous injection of epinephrine (0.4 cc. of 1:1000) was given at 3:58 P.M.

Table 3B shows the effect of epinephrine on water and electrolyte excretion in Patient H after he had been on a low-salt diet for three weeks. His urinary pH recording is also depicted in Figure 1 (Patient H-3). No

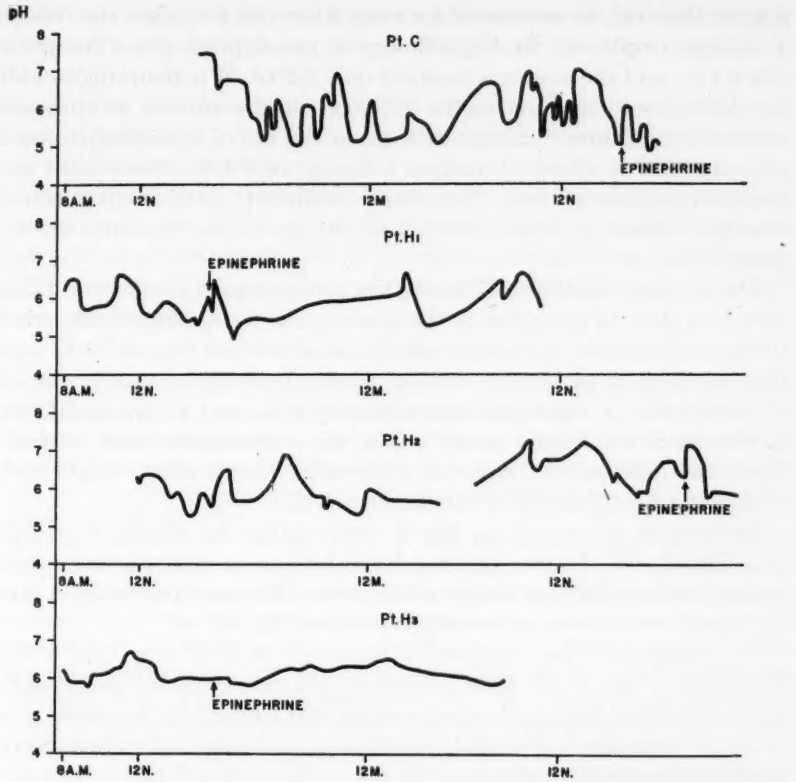

FIG. 1. Continuous urinary pH recordings from 2 patients. pH is plotted as the ordinate, and time as the abscissa. Patient C had a slight hypertension and epinephrine administration caused, as also in Patient H (H-1 and H-2), an increase in the pH of the urine. The last graph shows the urinary pH in Patient H after he had been on a low-salt diet for three weeks. It will be noted that the diurnal variations in pH are much less pronounced and that no increase in pH followed administration of epinephrine.

increase in urinary pH was observed following the administration of epinephrine. The increase in electrolyte excretion, in absolute terms, was negligible. This increase, however, was identical percentagewise with the increase in the earlier experiments in which the patient's salt intake was normal.

DISCUSSION

The pronounced differences in sodium and potassium excretion and water diuresis following epinephrine administration in the normal students, compared with those seen in the 2 patients on a normal salt intake, appear

greater than can be accounted for even when one considers the difference in dosages employed. Since the dosage of epinephrine given the patients was 0.4 cc. and the students received only 0.2 cc., it is tempting to ascribe the difference in reaction to the difference in the amount of epinephrine administered. Three students were given 0.4 cc. of epinephrine and had pronounced side effects; therefore a dosage of 0.2 cc. was chosen as the standard amount. These 3 students exhibited inconsistent electrolyte changes, similar to those observed in the group that received 0.2 cc. of epinephrine.

The obvious difference between the two groups was that the patients were in a state of rest prior to the administration of epinephrine, whereas the students carried on normal activity. It also seems reasonable to assume that the lack of agreement among various investigators as to the effect of epinephrine on water and electrolyte excretion may be due to differences in the basal conditions under which the experiments were performed. Thus, the difference in response observed in the students might well be explained by a difference in adrenergic activity.

Patients on a low-sodium diet do not exhibit any variation in urinary pH (Fig. 1) (7). In our study, administration of epinephrine to such a patient had no effect on the pH of the urine. The same patient on a normal salt intake exhibited a pronounced increase (Fig. 1).

It is suggested that changes in adrenergic activity may play a role in the alkaline tides of the urine, especially the one which follows awakening in the morning. Here a change in water and electrolyte excretion is seen, which is very much like that observed in a resting individual following epinephrine administration.

The increase in excretion of sodium, potassium, phosphate, sulfate and chloride can occur despite a decrease in output. This was observed in Patient C, indicating that the epinephrine effect is not due simply to an increase in filtration.

SUMMARY

The effect of epinephrine, administered subcutaneously, on urinary pH and on water, sodium and potassium excretion was studied in 10 normal, active subjects and in 2 patients. One of the patients received epinephrine twice within an interval of three days, during a period of high-salt intake. A third epinephrine injection was given the same patient after a three-week period of severe salt restriction.

Eight of the 10 normal subjects reacted to epinephrine with an increase in urinary pH, and 7 of the 10 exhibited diuresis. Changes in sodium and potassium excretion were inconsistent.

In the three experiments with patients on a normal salt intake, epinephrine caused a pronounced increase in the pH of the urine, as well as water and electrolyte diuresis.

The patient who had been on a low-salt diet showed practically no changes in urinary electrolyte and water excretion following epinephrine. Urinary pH did not change.

It is suggested that the difference between the reactions observed in the normal subjects and in the patients may depend upon the difference in their adrenergic activities. It is further proposed that changes in adrenergic activity may play a role in the pattern of the diurnal rhythm of water and electrolyte excretion.

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X-RAY TREATMENT OF MALIGNANT EXOPHTHALMOS: A REPORT ON 28 PATIENTS*

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TWO years have elapsed since the author reported some success in the treatment of 10 patients with "malignant exophthalmos" by irradiation of the pituitary (1). It was emphasized that the x-ray ports overlapped some extraocular soft tissue and that the resultant radiation to extraocular tissues might conceivably account for some or all of the beneficial effects observed, through decreasing the volume of these tissues. At least two articles have appeared since this publication confirming the effectiveness of x-ray therapy directed to the region of the orbits (2) and the pituitary (3) in 7 and 8 patients, respectively. We have now treated 18 more patients and have continued to follow those previously treated. When a larger number of patients with the disease have received this form of therapy and have been meticulously followed for a sufficiently long period of time, a better estimate may be made of the effectiveness of this procedure. More important, correlation of response may be made with other features of malignant exophthalmos, so that candidates for x-ray therapy may be selected more intelligently. Although our observations at present are based on only 28 patients so treated, the accumulated data suggest answers to these problems that might warrant consideration by others who encounter such patients in practice.

METHOD

All patients treated presented two or more eye signs of malignant exophthalmos. These signs previously (1) have been listed as increasing Hertel exophthalmometer measurements, plus one or more of the following: lid edema, bulbar conjunctival edema, limitation of extraocular muscle movement of the eyes, inability to close the eyes, and corneal ulceration. Generally, patients were selected for x-ray therapy because loss of vision

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was imminent. Nine of the 13 patients who later responded to x-ray therapy and 11 of the 15 patients who later showed no response had had a preliminary trial of desiccated thyroid. All patients, whether taking desiccated thyroid or not, showed progression of their exophthalmos immediately prior to x-ray therapy. The 13 patients responding to x-ray treatment ranged in age from 32 to 66 years, averaging 46 years. The 15 who did not respond ranged in age from 28 to 55, averaging 40 years. The numerical spread on each side of these average figures was quite uniform. Nine women and 4 men were in the responsive group and 9 and 7, respectively, were in

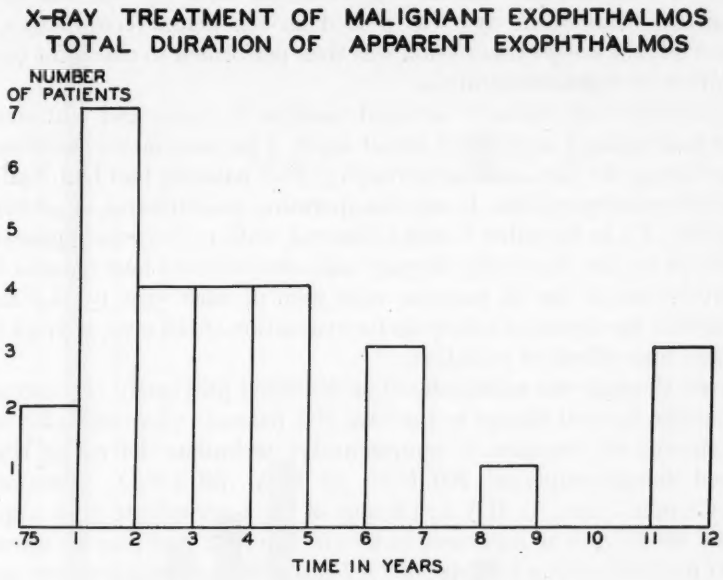

FIGURE 1

the non-responsive group. The time from the patient's first definite signs of exophthalmos to the time of our last observations ranged from nine months to twelve years, with the median around two to five years, as shown in Figure 1. In the average patient in both groups ("responders" and "non-responders") Hertel exophthalmometer measurements were obtained at three-month intervals, in the afternoon, by a member of the Ophthalmology Department, using the same baseline in consecutive measurements on a given patient. An average of 10 evenly spaced measurements were recorded on each patient during the time of this study. The period of exophthalmometer measurements averaged 28.8 months, ranging from 6 to 87 months. The degree of lid and bulbar conjunctival edema was estimated

by the ophthalmologist and the author independently on each visit and recorded in the range of + to ++++. The estimation of the degree of bulbar conjunctival edema was aided by gentle pressure of the examiner's finger against the lower lid as it was moved up toward the upper lid. The conjunctival edema fluid bulged out immediately preceding the eyelid. The degree of limitation of extraocular motion was estimated and graded as + for blurring of vision or diplopia (with or without minor objective findings) to ++++ for marked deviation of the ocular axis. The patient was also asked to close his eyes gently. The palpebral fissures were then measured vertically and the findings recorded when the lids did not approximate. Fluorescein dye was placed on the ocular conjunctiva and washed off; slit lamp examination was then performed to check for corneal ulceration or exposure keratitis.

Adjunctive local therapy included vaseline or boric acid ointment on gauze pads applied to eyes and lids at night, ¼ per cent methylcellulose eye drops during the day, and tarsorrhaphy. Two patients had had Naffziger decompression operations. In one the operation was bilateral, as previously described (1); in the other it was unilateral, with no response apparent in either eye by the time x-ray therapy was administered four months later. Twenty-seven of the 28 patients were seen at each visit by the author throughout the course of follow-up for evaluation of the eyes, thyroid function and toxic effects of radiation.

X-ray therapy was administered as described previously (1), except for an increase in total dosage in the case of 3 patients who responded and 3 who showed no response. A representative technique delivering this increased dosage employed 200 K.V., 25 M.A., 50 T.S.D., filtration 0.5 mm. Cu plus 1 mm. Al, H.V.L. 1.0 mm. of Cu, r per minute in air approximately 44–46, 150 as measured in air to each field each day to a total of 1500 r per field, with a field size of 8×7 cm. over each temporal area lateral to the pituitary. X-ray therapy was given under the direction of Dr. Isadore Lampe, Department of Roentgenology.

RESULTS AND DISCUSSION

The only untoward effects of x-ray to the pituitary in patients with malignant exophthalmos have been temporary preauricular epilation, serous otitis, abnormal taste sensation, mild headaches, and increase in ocular edema in one patient lasting twenty-four hours and disappearing when the total daily dose of x-ray was decreased. No evidence of hypopituitarism has appeared in these patients followed as long as eight years after irradiation.

Thirteen of 28 patients with malignant exophthalmos treated with x-ray to the region of the pituitary showed a significant favorable response in

exophthalmometer measurements, *i.e.*, 2 millimeters or greater in at least one eye, except for 2 patients who were included in this group because they simultaneously showed a decrease of 1.5 mm., plus disappearance of corneal ulcerations and decrease in ocular edema. The actual exophthalmometer response in millimeters in each patient is shown in Figure 2. The

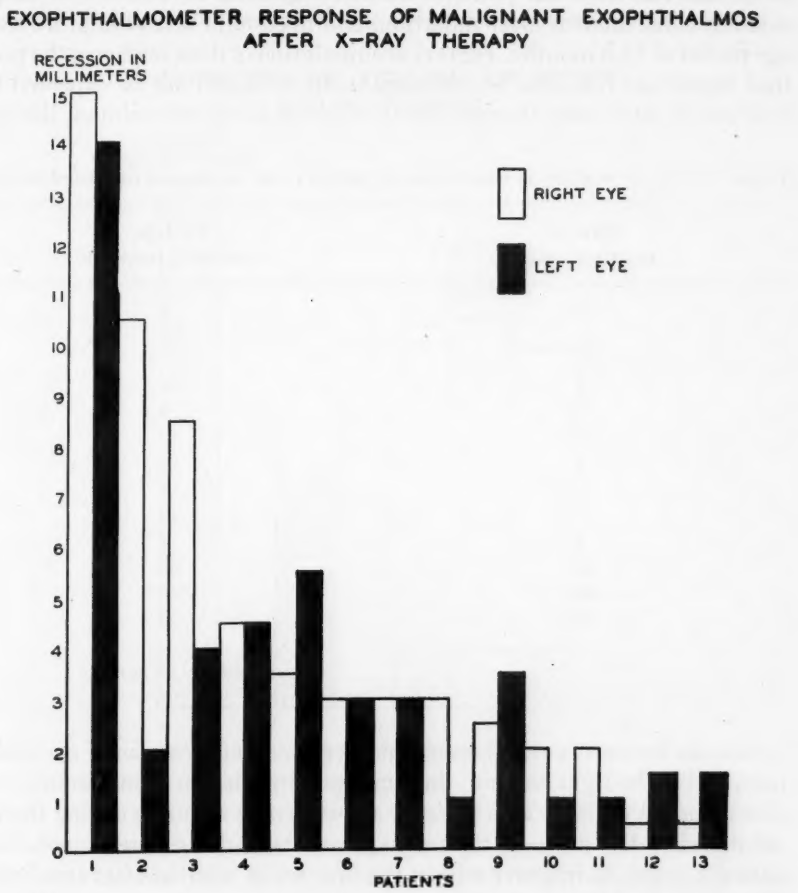

FIGURE 2

open bar shows the exophthalmometer response in millimeters for the right eye (O. D.), and the adjacent solid bar, for the left eye of that patient (O. S.). It should be noted that 2 patients showed responses as great as 15 and 10 mm. This seems important, because our review of the literature reveals no responses of this magnitude occurring "spontane-

ously" or with desiccated thyroid. The median response, as indicated in Figure 2, was about 3–4 mm.

The point was made in a previous publication (1) that the radiation therapist and clinician in the past usually re-evaluated these patients one month after treatment had been administered. A change is unlikely in this short interval, since our patients showed beginning of recession of exophthalmos three months after radiation, and maximum recession at an average period of 11.8 months. Further accumulation of data reaffirms the point that significant recession of the exophthalmos should not be expected the first month after x-ray therapy. Table 1 shows, in the left column, the time

TABLE 1. TIME IN MONTHS BETWEEN X-RAY THERAPY AND RECESSION OF EXOPHTHALMOS

Start of recession noted	To date, maximum recession
0	5
1	54
3	7
3	13
3	6
3	13
3	11
4	14
4	42
7	7
14	36
20	20
24	24
	—
	Average = 19 months

in months between x-ray therapy and beginning of recession of exophthalmos, and in the right column, the time from irradiation to maximum recession recorded to date. Two patients showed some response during the first month after the start of treatment, 1 of these during treatment. Most patients began to improve within the first seven months after irradiation. That not all of those who respond favorably start to improve within the first seven months after x-ray therapy, however, is shown by the fact that 3 patients were exceptions to this seven-month rule, in that they were noted to respond after a fourteen-month interval. A patient recorded as showing the start of recession of exophthalmos at twenty-four months actually noted marked improvement before this, but returned for a check-up at twenty-four months, at which time dramatic improvement was noted,

including a decrease in measurements of 15 mm. O. D. and 14 mm. O. S. Two of these 3 patients who were exceptions to the seven-month rule apparently started to respond at twenty- and twenty-four months. "Spontaneous" regression might have been the cause of improvement in these 2 patients. This possibility seems unlikely, however, in that many patients were followed up to four years after x-ray therapy without showing "spontaneous" regression of exophthalmos. Incidentally, the relatively large

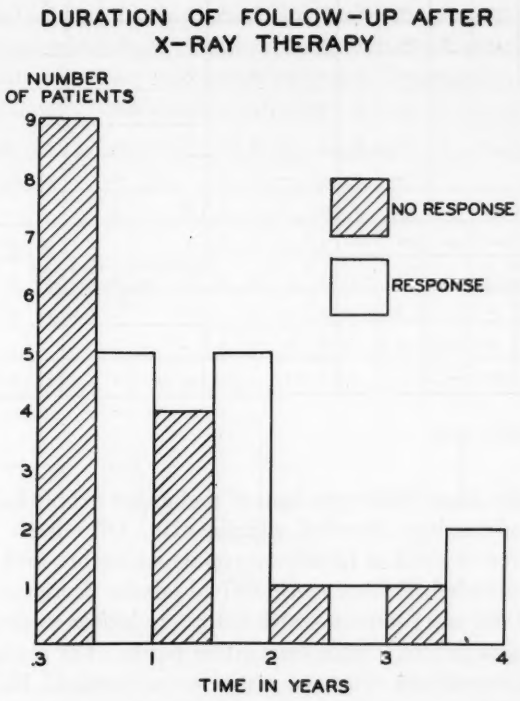

FIGURE 3

number of those who did not respond, seen in Figure 3 to have been followed less than one year, indicates that some of these patients might later return significantly improved. In retrospect, they might then be found to have shown beginning response during this first year.

Table 2 shows the correlation between exophthalmometer measurements and other eye signs before x-ray therapy and after maximum response in measurements. The eye signs so correlated are lid edema, bulbar conjunctival edema, extraocular movements (E.O.M.), palpebral fissures in terms of millimeters with eyes "closed," corneal ulceration, and tonometer ten-

TABLE 2

CORRELATION OF EXOPHTHALMOMETER MEASUREMENT RESPONSE WITH RESPONSE OF OTHER EYE SIGNS OF MALIGNANT EXOPHTHALMOS BEFORE X-RAY AND AFTER MAXIMUM RESPONSE OF MEASUREMENTS

PATIENT	LID EDEMA		BULBAR EDEMA		EXTRA-OCULAR MOVEMENTS		PALPEBRAL FISSURE IN MM. WITH EYE "CLOSED"				CORNEAL ULCERATIONS				TONOMETER TENSION				MM. RECESSION BY EXOPHTHALMOMETER MEASUREMENTS	
	BEFORE	AFTER	BEFORE	AFTER	BEFORE	AFTER	BEFORE O.D.	BEFORE O.S.	AFTER O.D.	AFTER O.S.	BEFORE O.D.	BEFORE O.S.	AFTER O.D.	AFTER O.S.	BEFORE O.D.	BEFORE O.S.	AFTER O.D.	AFTER O.S.	O.D.	O.S.
C.B.	++	++	++	++	++	++	3	5	3	5	0	0	+	+++	22	20			3.0	1.0
O.C.	++++	++	+++	+	++	0	5	4	3	3	++	++	+	+	N*	N	N	N	4.0	5.0
S.G.	+++	0	++	0	+++	0	0	2	0	0	0	0	0	0	--	--	--	--	3.0	3.0
H.J.	++	+	++	0	++	0	2	1	0	0	+	++	0	0	24	24	N	N	2.0	1.0
M.L.	++	+	++	+	+++	0	2	3	1	1	+	+	0	0	--	--	--	--	.5	1.5
M.N.	+++	++	0	0	0	0	0	0	0	0	+	+	0	0	20	20	--	--	.5	1.5
E.M.	+	+	+	+	+++	0	--	--	--	--	0	+	0	0	20	23	14	14	3.5	5.5
C.P.	++++	+	+++	0	+++	0	--	--	--	--	0	0	0	0	--	--	--	--	15.0	14.0
H.R.	+++	++	+++	+++	++++	++++	3	3	3	3	0	0	+	+	22	22	23	23	2.0	1.0
B.S.**	+++	—	+	—	0	++++	0	0	0	0	+	+	0	0	20	20	--	--	2.5	3.5
M.S.	++	0	++	—	0	0	9	8	0	0	--	--	--	--	20	20	--	--	10.5	2.0
N.T.	++	0	++	0	--	--	0	0	0	0	--	--	--	--	--	--	20	20	8.5	4.0
M.V.	++++	+++	+++	++	+++	0	2	3.5	--	--	+	++	0	0	43	32	17	17	3.0	3.0

* Normal
**Olivo-ponto-cerebellar atrophy

sions. Generally, these other eye signs of malignant exophthalmos improved when the exophthalmos receded significantly. Lid edema decreased in 7 and disappeared in 3 out of 12 patients on whom before-and-after measurements were recorded. Bulbar conjunctival edema decreased in 3 and disappeared in 4 out of 11 patients with before-and-after records. No patients showed a progression of edema during this period. The majority of limited extraocular movements returned entirely to normal. The only patient (B.S.) showing increased limitation of E.O.M. during this interval had an accompanying neurologic condition diagnosed as olivo-ponto-cerebellar atrophy, present for many years before treatment (1). It was expected that the receding globe would allow the lids to approximate during sleep, but exceptions were observed. Corneal ulcerations usually disappeared, but not infrequently reappeared for short intervals during regression in the exophthalmometer measurements. Tonometer tensions were not usually markedly elevated, but were alarmingly high in patient M. V., who was at first treated with miotics for glaucoma, but no longer needed treatment when her tonometer tensions fell well within the normal range with decrease in her exophthalmos. It should be noted that patients showing the

greatest response in exophthalmometer measurements did not necessarily show the greatest improvement in other eye signs. Improvement in other eye signs in most patients, however, did become apparent when significant improvement in the exophthalmometer measurements was recorded.

Important correlations that should be looked for in this study concern factors in treatment response that might aid us in the future in choosing the patients with malignant exophthalmos most likely to enjoy a favorable response to radiation. For example, must the exophthalmos be of short duration if the patient is to profit from x-radiation? Our data suggest that malignant exophthalmos usually responds to irradiation if it has been present less than one year, and rarely responds if present more than two years. Jones (2), with some success, directed x-rays to the orbital region,

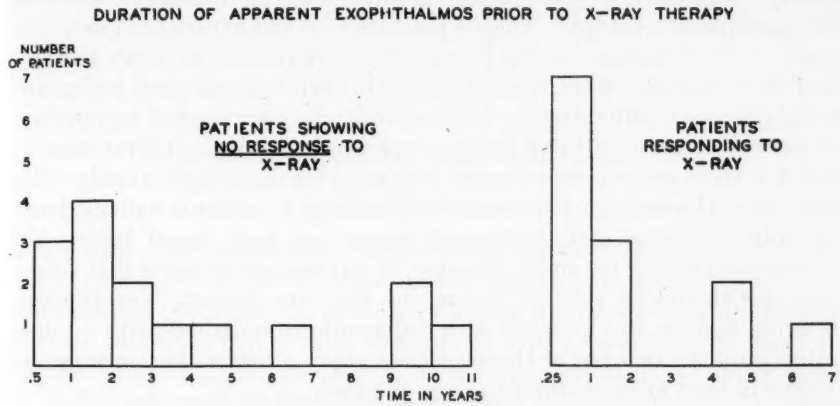

FIGURE 4

rather than to the pituitary. His rationale was that the cells forming the orbital infiltrations were of a type regarded as highly radiosensitive, and the resolution of similar chronic inflammatory reactions elsewhere was known to be favorably influenced by irradiation. This reaction, microscopically simulating a chronic inflammatory process, occasionally has been followed by a condition in which the extraocular muscles consisted of nothing but fibrous tissue (4, 5, 6). Dobyns (7) notes that "these differences in pathologic findings seem to be in keeping with the various stages of the pathologic process, ranging from an acute reaction to chronic fibrosis." The fibrous replacement of retro-orbital and peri-orbital tissue late in the disease might furnish a logical explanation for Friedgood's observation (8) that long-standing exophthalmos was less reversible than that of shorter duration. The majority of patients whose exophthalmos receded after x-ray therapy (Fig. 4) had had apparent exophthalmos for less than one

year. Only 3 patients whose exophthalmos was of more than two years' duration showed response. None of our patients who had had exophthalmos over seven years responded to x-ray treatment. Only 3 of the 15 who did not respond had had apparent exophthalmos for one year or less prior to x-ray therapy.

If we assume that malignant exophthalmos is caused by increased action of the thyroid-stimulating hormone on the periorbital tissues, it would seem worthwhile to correlate response after x-ray with the status of the thyroid at the time of x-ray treatment. Four patients in the responsive group exhibited no evidence of thyroid disease. All of those who did not respond, on the other hand, had a history of thyrotoxicosis. Patients in whom exophthalmos developed after thyroidectomy for thyrotoxicosis were relatively evenly distributed between the two groups—5 in the responsive, and 7 in the unresponsive category. Only 4 patients who had experienced development of exophthalmos during thyrotoxicosis responded to x-ray therapy and these patients were treated for both thyrotoxicosis and malignant exophthalmos simultaneously. In 8 patients who later showed no response to x-ray treatment, the exophthalmos had developed during thyrotoxicosis, and 6 of these patients were treated with x-ray for their exophthalmos while still toxic. This resistance to treatment exhibited by patients with evidence of both thyroxine and thyrotropin excess has been noted before (9). These numbers are too small, however, to warrant a conclusion that thyrotoxicosis should be relieved before the eyes are treated. Nevertheless, it is our opinion that patients with malignant exophthalmos with no definite symptoms or signs of thyrotoxicosis enjoy a better than average response of their exophthalmos to x-ray therapy.

If increased thyroid-stimulating hormone activity is responsible for the development of malignant exophthalmos, and if the hyperfunctioning pituitary is more responsive to x-ray therapy than the normally functioning pituitary (10, 11), then the depression of TSH production or release produced by the administration of desiccated thyroid (12, 13) might render patients who are treated with thyroid less responsive to x-ray. Figure 5 shows, however, that desiccated thyroid was administered to about the same number of patients for the same period of time, both in patients responding and in those not responding to x-ray therapy.

SUMMARY AND CONCLUSIONS

1. Twenty-eight patients with malignant exophthalmos were treated with x-rays directed to the region of the pituitary gland. Thirteen of these showed a significant response in exophthalmometer measurements after this treatment.

2. Eleven of these 13 patients, in retrospect, began to show response

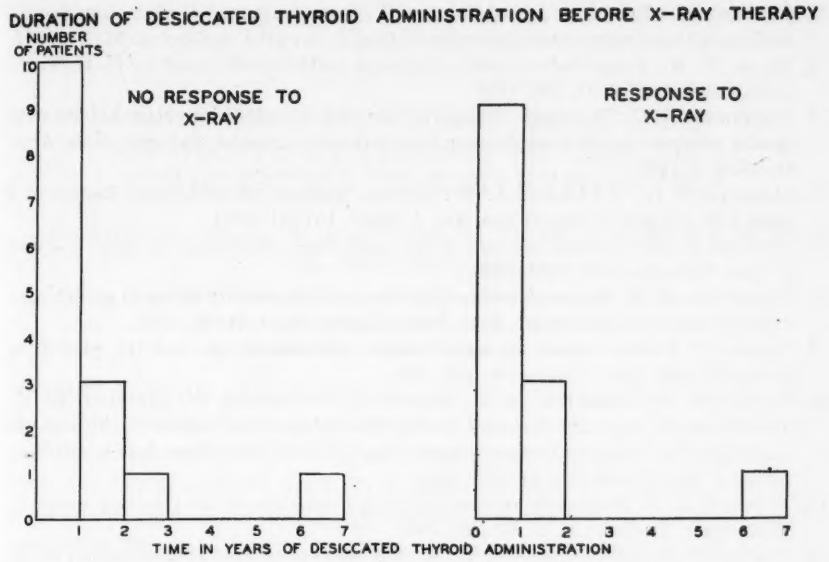
DURATION OF DESICCATED THYROID ADMINISTRATION BEFORE X-RAY THERAPY
NUMBER OF PATIENTS
NO RESPONSE TO X-RAY
RESPONSE TO X-RAY
TIME IN YEARS OF DESICCATED THYROID ADMINISTRATION

FIGURE 5

in less than seven months after x-ray therapy, but this response was usually not apparent within the first month after therapy. Maximum recession of the eyes reached a median of about 3–4 mm. during the nineteen-month average follow-up period after irradiation, with a maximum recession of 15 mm. in one patient and 10 mm. in another. Generally, other eye signs of malignant exophthalmos improved when the exophthalmos receded significantly.

3. Our data suggest that malignant exophthalmos usually responds to x-ray therapy of this type if the exophthalmos has been present less than one year, but rarely responds if it has been present more than two years.

4. Patients with coexistent thyrotoxicosis and malignant exophthalmos had exophthalmos which was more resistant to treatment than that of patients without active thyrotoxicosis.

5. No difference was found in the responses of exophthalmos to x-ray therapy between the group of patients fed desiccated thyroid both before and during the period of irradiation and the group not fed thyroid.

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SUCCESSFUL TREATMENT OF A CASE OF CUSHING'S SYNDROME BY ELECTRO-COAGULATION OF THE HYPOPHYSIS

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IRRADIATION of the pituitary region, up to now, has been the non-surgical method of choice in the treatment of Cushing's syndrome not due to adrenocortical tumor. Good therapeutic results have been reported by a number of authors. Luft (1) described 7 cases of Cushing's syndrome treated by massive doses of x-ray; 4 showed a complete or almost complete remission. Sosman (2) reviewed 42 cases from the literature up to 1948; 9 showed a complete recovery. Plotz *et al.* (3) reported on 19 cases; 9 showed complete or partial improvement after irradiation. Johnsen (4), on the whole, had similar experiences with x-ray treatment.

The literature, however, contains a large number of reports on cases of Cushing's syndrome uninfluenced by x-ray treatment. It is a matter of discussion whether some of these cases received insufficient dosage. The duration of the therapeutic effect is difficult to judge from the reports in literature, but permanent improvement has been observed.

During recent years an approach to surgical treatment of Cushing's syndrome has been made. In this connection reports by Pattison and Swan (5) and later by Northfield (6) should be mentioned. They inserted radon seeds into the pituitary, with some curative effect. Subtotal adrenalectomy has been performed with therapeutic success in a fairly large number of cases (7).

The present study demonstrates another approach to the treatment of Cushing's syndrome. An attempt was made to destroy the hypophysis in order to abolish the presumed hypersecretion of the adrenocorticotropic hormone.

CASE REPORT

The patient was an unmarried woman, born in 1927. She was in good health during childhood and early adolescence until 1942, when she started to gain weight and to complain of fatigue and increasing pains in the back and head. A full-moon face, hypertri-

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chosis and purplish striae rapidly developed. She had not yet reached menarche in 1943.

Examination in May **1943**: Her body weight was 57 Kg. and body length, 154 cm. She demonstrated typical Cushing's syndrome with truncal obesity, sparing the extremities, and a typical "buffalo hump." The face was plethoric (full-moon), the breasts very small, and there was pronounced thoracic kyphosis. She had moderate hypertrichosis, the hair on the head was dry and thin, the skin on the extremities was rough and squamous and also showed acrocyanosis, numerous small purplish striae and an increased tendency to bruise. She complained of headaches, weakness and backache and became breathless even on slight exertion. The uterus was the size of a thumb. X-ray examinations of the back did not reveal any significant osteoporosis. The blood pressure was 130–150/80–90 mm. of Hg and the BMR's were −18 and −10 per cent. Dextrose tolerance was reduced. X-ray examination of the adrenals after perirenal insufflation of air gave normal findings. Laparotomy disclosed enlarged ovaries with numerous follicles and cysts.

The patient received two courses of irradiation of the hypophysis—one in July and one in November 1943; 1500 r were given in each of the two series.

The patient was re-examined in October, February and July 1944. A rapid improvement was obvious after the first series of treatments. All symptoms had disappeared by the beginning of 1944. The first menstruation appeared in November 1943. She then menstruated regularly for several years. The disease was considered to be in complete remission. In July 1944 the body weight was 51 Kg. and the body length, 154 cm.

Symptoms of Cushing's syndrome reappeared during the spring of 1948. When re-examined in August 1948 she again showed full-blown Cushing's syndrome, more advanced than in 1943. In September 1948 she was again treated by irradiation of the hypophysis. There was some temporary improvement, but at re-examination in March 1950 the disease was still more advanced. She was given massive doses of x-ray (4500 r) in April 1950, with no appreciable effect.

Examination in May–July **1951** (Fig. 1): The patient had not been able to work since 1948. She suffered from headaches, severe backache and marked fatigue, and became breathless on the slightest exertion. She had cardiac asthma but no edema. She was confined to bed for most of the day and used large doses of analgesics. No menstruation had occurred since February 1948.

At examination she showed advanced Cushing's syndrome with marked obesity of the buffalo type, thin extremities and a full-moon face. Body weight was 70 Kg. and body length, 155 cm. At this time the hypertrichosis was much more pronounced and localized to the face, thorax, abdomen and extremities. She had a large number of purple striae on the hips and abdomen, ecchymoses, and severe acne of the face and upper thorax. Blood pressure at rest was 200/130 mm. of Hg and the heart was enlarged to the left; there were no signs of circulatory failure at bed rest. The findings on neurologic examination were normal.

For laboratory findings, see Table 1.

Electrocoagulation of the pituitary gland was performed on June 26 and July 6, 1951. The pituitary region was exposed by a rather small pituitary flap, and the arachnoid in the chiasmal cistern removed as completely as possible. The hypophysis was then electrocoagulated with an electrode, insulated up to 5 mm. from its tip, in seven different places during the first operation and in thirteen during the second one.

The postoperative course was uneventful. She no longer appeared plethoric after two weeks. The blood pressure showed a gradual decline, and was found to be 120-130/80–90 mm. of Hg one month after the operation. By this time the heart volume had decreased from 460 to 390 cu. cm./sq. M. of body surface. The color of the skin was nor-

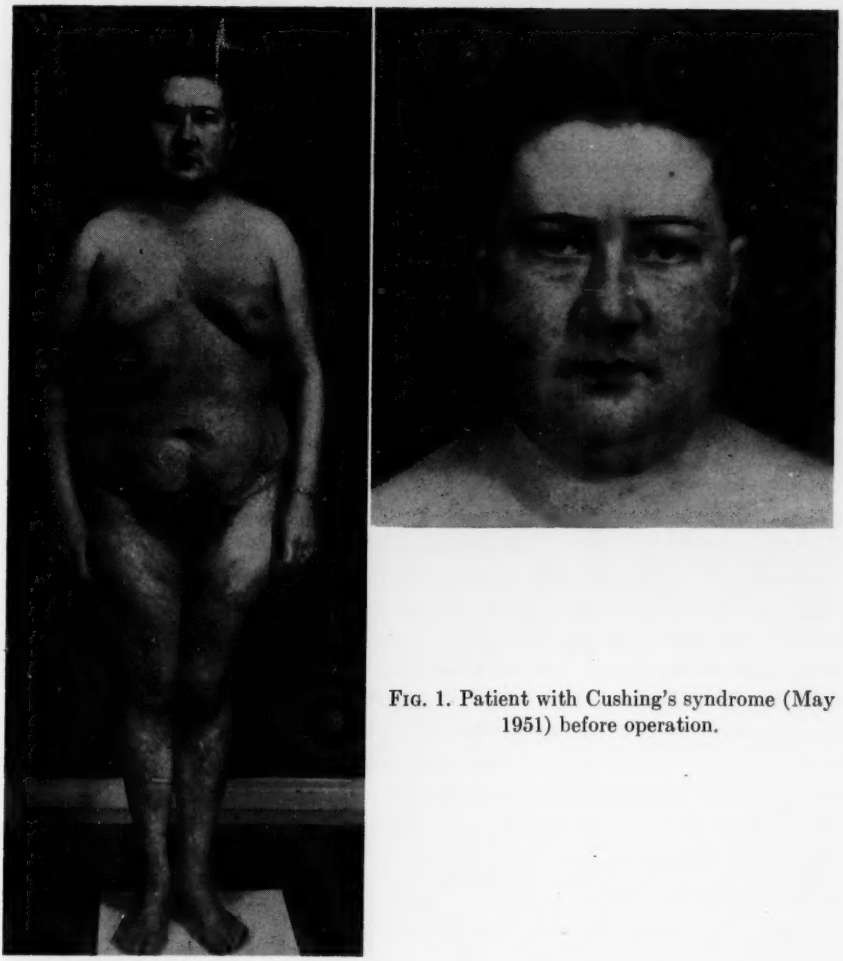

FIG. 1. Patient with Cushing's syndrome (May 1951) before operation.

mal, and the acne and ecchymotic tendency had disappeared. Body weight had decreased by 10 Kg. (the patient was kept on a low caloric diet). *Three weeks after the last operation she had her first menstruation in three and a half years.* Menstruation has remained regular since. She continued to lose weight, and her habitus became normal.

At re-examination in November 1951 a slight hypertrichosis was the only remaining symptom. The patient was re-examined on two further occasions: *in April and October 1952.* She remained healthy without any symptoms of her previous disease and was able to work around the house for limited periods of time. No substitution therapy was given. The pains in the back and head disappeared. However, her psychic condition left much to be desired. She was psychasthenic and had difficulty in concentrating on a task. She had for many years been used to sedatives and analgesics and still used them frequently.

She became pregnant in August 1952, and a legal abortion was made in December. Menstruation reappeared in January 1953.

Tables 1 to 3 give a review of the clinical and laboratory findings before and after the operation. Figures 1 and 2 demonstrate her body changes.

TABLE 1. LABORATORY FINDINGS BEFORE AND AFTER OPERATION
(Operation performed in July 1951)

	May 1943	July 1944	May 1951	August 1951	November 1951	April 1952	October 1952
Blood pressure, mm. Hg	140/90	110/70	170–200/120–135	120–130/80–90	115/85	115/70	120/75
Heart volume, cu. cm. /sq.M. body surface			460	390	350		310
BMR, %	−14	+4	−12	+6	−4	−10	+4
17-Ketosteroids, mg./24 hrs.			7–12	1–6	2–6	6	3–4
Reducing corticoids, mg./24 hrs.*			1.7–3.7	0.7–1.5		1.0–1.3	0.9–1.5
ACTH test; eosinophils			86→25	279→128	1210→360 1100→430	200→67	357→66
Adrenaline test; eosinophils				296→259 665→444	1080→740 710→453	142→75 180→70	407→289
Eosinophils—lymphocytes, % in diff. count			eos. 0–1 ly. 0–1	eos. 18–20 ly. 16–26	eos 17–21 ly. 31	eos. 1 ly. 52–59	eos. 10 ly. 39
Cholesterol, mg. per 100 cc.			270	295	330	200	250
CO_2 capacity, vol. per cent			65	48	50		
Plasma phosphorus, mg. per 100 cc.			3.1	4.4	4.8	4.4	3.7
Creatine in urine, mg./24 hrs.			126	0	0	30	0
Calcium in urine, mg./24 hrs.			160–316	65–237		32	30
Two-dose, 1-hour dextrose tolerance test; blood sugar, mg. per 100 cc.			101-163-226 glycosuria?		84-108-113 102-156-127	94-200-205	82-138-127
Insulin tolerance test			normal	normal	normal	normal	normal
Water load test (1000 ml.)†			995 ml. 1.003–1.017	625 ml. 1.004–1.022		600 ml. 1.004–1.027	810 ml. 1.003–1.018
Adrenaline in urine, μg./24 hrs.			5.5–11		8.7		4.6
Nor-adrenaline in urine, μg./24 hrs.			45–55		29		24
Glom. filtration rate/renal blood flow, ml./min.			84/504			98/476	
I^{131} test; excretion in % of dose,							
1-day			46				45
2-day			2				1

* Determined by a modification of a method described by Sprechler (9): normal range 1.0–1.5 mg. per day.

† The first figure denotes the urine volume during the first four hours, the second and third figures the lowest and highest specific gravity of the urine during the test.

DISCUSSION

The diagnosis of Cushing's syndrome in the present case is beyond question. All cardinal symptoms were present in 1943, they reappeared and were still more pronounced in 1948, and progressed up to the last preoperative examination in 1951. The increased excretion of reducing corticoids in 1951 confirms the diagnosis. Adrenocortical tumor was excluded in 1943 by means of perirenal insufflation of air and palpation of

TABLE 2. BODY MEASUREMENTS BEFORE AND AFTER OPERATION
(Operation performed in July 1951)

	May 1943	July 1944	February 1950	July 1951	November 1951	April 1952	October 1952*
Body weight, Kg.	57	52	68	63	53	46	50
Neck, cm.	38.5	32.5	37.5	37	35	33	32
Chest, cm.	93	82	98	100	86	81	85
Abdomen, cm.	90	73	96	97	79	70	74
Hips, cm.	92	87					
Thighs, cm.				48	47	48	44
Calves, cm.	32	33.5	31	29	30	29	29
Upper arms, cm.	26	26	26	26	25	23.5	24.5
Forearms, cm.	19	20.5					

* Pregnant.

the adrenal glands at an exploratory laparotomy. Biopsy specimens from the ovaries showed some cystic degeneration.

As has already been mentioned, repeated irradiation of the pituitary region with large roentgen doses has in many cases stopped the progress of the disease and even made the symptoms disappear completely. However, a survey of the pertinent literature as well as our own experience shows that many cases do not react favorably even to repeated series of irradiation. In our opinion, the initial treatment in a case of Cushing's

TABLE 3. CLINICAL FINDINGS BEFORE AND AFTER OPERATION
(Operation performed in July 1951)

	May 1943	July 1944	May 1951	August 1951	November 1951	April 1952	October 1952
Obesity of the trunk	++	−	+++	++	−	−	−
Full-moon face	++	−	+++	+	−	−	−
Acne	++	−	++	+	−	−	−
Purplish striae	++	−	+++	++	−	−	−
Bruisability	++	−	++	+	−	−	−
Hypertrichosis	++	−	++	++	+	+	(+)
Menstruation	−	+	−	+	+	+	pregnant
Circulatory failure	++	−	++	−	−	−	−
Osteoporosis	+?	−	−	−	−	−	−
Asthenia	++	−	+++	++	+	+	++
Headaches	++	−	+++	+	−	−	−
Back pain	++	−	+++	+	−	−	−

syndrome without adrenocortical tumor should, in any event, consist of irradiation of the pituitary region with massive roentgen doses.

The rationale of the surgical treatment of Cushing's syndrome is to reduce the amount of secreting adrenocortical tissue. Total or subtotal adrenalectomy has in many cases been followed by a complete remission. Subtotal adrenalectomy seems at present to be the most promising treatment of Cushing's syndrome. Cortisone has to a great extent made this procedure possible.

In the present case we made an attempt to destroy the hypophysis in order to reduce adrenocortical function. However, the operation showed that even a *reduction* of the amount of pituitary tissue was sufficient to cause a remission of Cushing's syndrome.

Electrocoagulation of the hypophysis was performed on two occasions, with an interval of ten days. As the excretion of reducing corticoids increased markedly some days after the first coagulation and all symptoms further remain unchanged, a second and more extensive coagulation was performed. The second operation induced a rapid improvement that was obvious after ten days.

The extraordinary resistance of at least healthy pituitary tissue should be noted, as the hypophysis was still functioning despite some twenty single coagulations, each comprising the volume of a small pea (as tested on a piece of meat). Under such circumstances it is also obvious that a small amount of glandular tissue is sufficient for the maintenance of an apparently normal endocrine status.

Within one month after the second operation, the patient had her first menstruation since 1948. On the whole, the periods remained regular until September 1952, when she became pregnant. No depression of thyroid function was noted up to the time the patient was last seen, *i.e.*, no clinical signs of hypothyroidism; the BMR and the urinary excretion of tracer doses of radioiodine were within normal limits. It was more difficult to assess the adrenocortical function, but all tests gave normal results: the excretion of 17-ketosteroids was low normal, the excretion of reducing corticoids was normal, ACTH and adrenaline caused a normal lowering of the number of circulating eosinophils, and excretion of a water load was not delayed. The insulin tolerance was not decreased, normal amounts of adrenaline and nor-adrenaline were excreted, and the CO_2 capacity of plasma was unchanged. An increased number of circulating eosinophils and an elevation of the serum phosphorus level were observed for a couple of months after the operation. This is noteworthy, as administration of ACTH causes a decrease in the number of eosinophils and in the concentration of serum phosphorus.

The patient had for many years suffered from hypertension, with en-

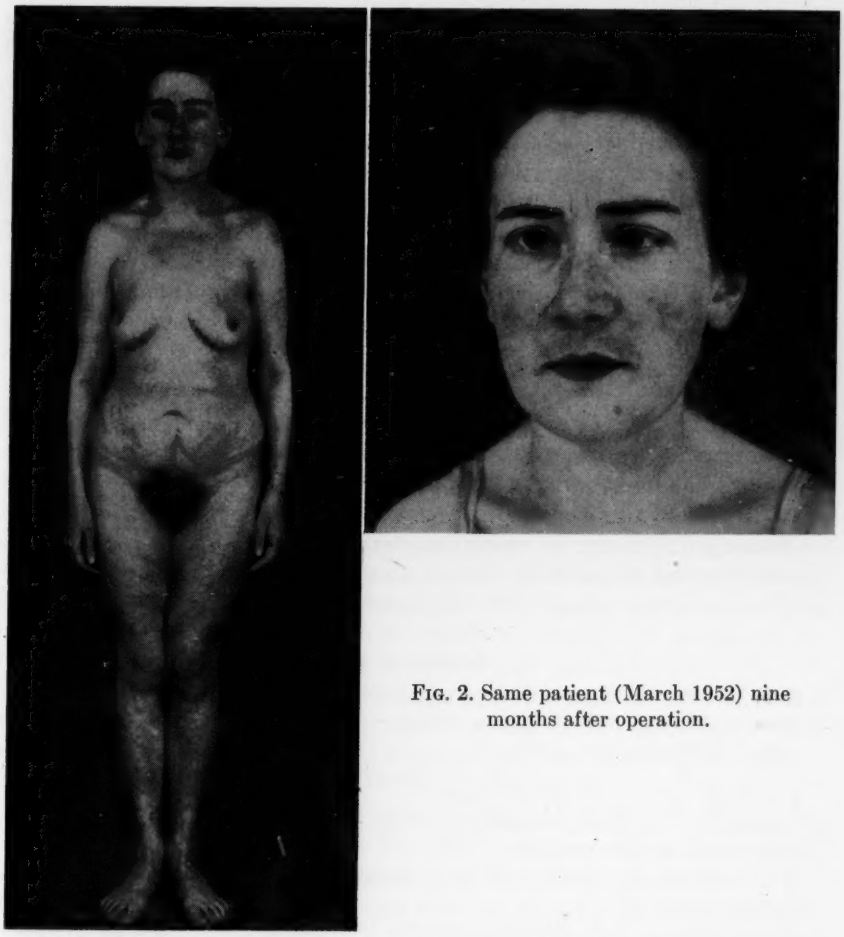

FIG. 2. Same patient (March 1952) nine months after operation.

largement of the heart, and with failing circulation for the last months. The clinical status shortly before the operation indicated a fatal outcome within a short period of time. It is therefore noteworthy that the blood pressure started to decrease during the first postoperative week and was normal within one month. All signs of circulatory failure had then disappeared, and there was no longer any enlargement of the heart.

The operation also brought about an increase in the dextrose tolerance, which became normal.

The pathogenesis of Cushing's syndrome has been thoroughly discussed by several authors (*see* Kepler (8)). Opinions differ as to whether a disturbed function of the hypophysis or of the adrenal cortex is the pri-

mary change. The result of the surgical intervention, *i.e.*, the clinical cure of the patient in association with a normally functioning hypophysis and adrenal cortices, strongly suggests the etiologic significance of the pituitary gland in the present case of Cushing's disease.

The following fact seems most puzzling to the authors: The pituitary tissue was certainly reduced—although not more than to permit a normal function of the adrenal cortex. Why then did the Cushing syndrome disappear? Is it possible that the abnormal cells were damaged selectively?

Finally, it should be mentioned that at no time did the patient show symptoms of diabetes insipidus. In view of the normal function of the peripheral endocrine glands, this demonstrates that the pituitary stalk was intact.

SUMMARY

A report is given on a typical and advanced case of Cushing's syndrome in a woman 24 years of age. She was treated by electrocoagulation of the hypophysis. The syndrome disappeared completely within a couple of months, and she is still healthy nineteen months after the operation. The electrocoagulation did not cause complete destruction of the gland, as the gonads, thyroid and adrenals showed normal function. The patient became pregnant fourteen months after the operation.

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QUANTITATIVE EFFECT OF CORTISONE UPON KETOSTEROID EXCRETION AND CLINICAL PICTURE OF THE ADRENOGENITAL SYNDROME*

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THE therapeutic approach to the management of adrenal cortical hyperplasia has encompassed a great many different concepts, dependent upon either the medical or surgical inclination of the therapist. Patients with Cushing's syndrome were first treated with different endocrine preparations in an attempt to ameliorate the syndrome physiologically by hormonal therapy antagonistic to the active principles elaborated from the hyperactive adrenal cortex (1–5). Subsequently, however, it was found that many cases of Cushing's syndrome could very effectively be treated surgically by the removal of part of each adrenal gland (6–9). On the other hand, in the adrenogenital syndrome or so-called masculinizing syndrome, the approach first was primarily surgical and only recently has the disease been treated medically with any degree of success through the use of hormonal therapy. The endocrine approach to therapy in the adrenogenital syndrome has been based upon the findings of Wilkins and his coworkers, who demonstrated that the administration of cortisone, intramuscularly or orally, could effectively inhibit the hypersecretion of 17-ketosteroid precursors from the adrenal cortex (10–14). These reports were mainly concerned with therapy in the juvenile adrenogenital syndrome. More recently Jones *et al.* (15) have described the same type of therapeutic approach in the adult patient, in whom particular attention was given to the effect of cortisone in problems of sterility. We should like to report on the response of a patient with a history of long-standing adrenogenital syndrome, who responded favorably to comparatively small doses of oral cortisone after therapeutic failure with estrogenic and progesterone compounds.

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CASE HISTORY

The patient was first examined at the age of 15 in 1930, at which time it was noted that she had a large clitoris, primary amenorrhea, increased facial and body hair, and a masculine habitus. This picture had been casually noted one year previously. At that time, in addition to the excessive hair growth which was male-like in distribution, a marked increase in the size of the clitoris was observed. Her clitoris measured 5 cm. in length and resembled an imperforate penis in every way, with a dimple instead of a urethral meatus at the distal end. The patient, did, however, have a vaginal introitus which would admit the tip of a small finger. The urethra appeared to be located in the anterior vaginal wall. Blood estrogen determinations made at this time by the bioassay method of Frank and Goldberger (16) showed evidence of only minimal estrogenic activity, *i.e.*, there was less than 1 m.u. per 50 cc. of blood. Full cornification was not attained in the assay animals with this amount of blood. Other laboratory findings were a normal glucose tolerance, and a BMR of −5 per cent. X-ray examination showed the skull and sella turcica to be normal, and there was no evidence of adrenal hyperplasia or tumor, by retrograde pyelogram. An exploratory laparotomy was performed two years later in 1932 when the patient was 17 years old, at which time it was found that although she had the usual female pelvic organs, the uterus, tubes and ovaries were definitely hypoplastic. Examination of the adrenals from the abdominal approach did not reveal any masses or evidence of hypertrophy. Since no testicular tissue was found, the only surgical procedure carried out at this time was an appendectomy and amputation of the hypertrophied clitoris. The patient made an uneventful recovery, following which she received cyclic therapy with estrogens to induce estrogen withdrawal bleeding in an attempt to compensate for her primary amenorrhea. Her response was adequate, as manifested by an increase in breast and uterine size, accompanied by uterine withdrawal bleeding. However, spontaneous menstrual periods without previous estrogen therapy were not recorded.

In 1935 and 1936 at the ages of 20 and 21, respectively, she received deep x-ray therapy to the adrenal regions, consisting of 4,600 R to each adrenal gland. Following this she responded with a spontaneous menstrual period, although estrogen had been withheld four months prior to radiation therapy. Subsequently, she received additional radiation therapy consisting of 2,000 R to each adrenal gland and again this was followed by three spontaneous, irregularly spaced menstrual periods. Since no further menstrual periods were noted, the patient was once more given estrogen at irregular intervals, to induce estrogen withdrawal periods. It became increasingly difficult, however, to induce a menstrual flow in the patient by such cyclic therapy. The administration of estrogen produced no detectable change in the hypertrichosis or body configuration. In 1939, at the age of 24, an elevated pregnanediol excretion in the range of 25.5 mg. per twenty-four hours was observed. (The gravimetric method of Venning and Brown was employed for the determination of pregnanediol glucuronide (17).) Despite this finding, very little therapy was undertaken between 1939 and 1947. In 1947 a fasting blood sugar level of 124 mg. per 100 cc. was noted. Insulin therapy, however, was not instituted and she was treated by diet only. In November 1947 the patient was again subjected to another extensive work-up, with an attempt being made to detect evidence of adrenal hyperplasia or neoplasm. Perirenal air insufflation with laminographic[1] study was carried out and

[1] Laminography and unilateral adrenalectomy were carried out by Dr. Seymour Wilhelm at the New York Beth Israel Hospital.

revealed evidence of bilateral adrenal hypertrophy. At this time the patient's ketosteroid excretion ranged between 52 and 89 mg. per twenty-four hours and the blood sugar level varied between 129 and 170 mg. per 100 cc. The left adrenal gland was removed[1] on January 15, 1948 and was reported as weighing 14 grams (normal 4–6 grams); histologically it revealed a deeply pigmented androgenic zone. Her postoperative course was somewhat stormy. A urinary tract infection developed, which required therapy with urinary antiseptics and was finally partially controlled by large doses of aureomycin. Since complete abeyance of the infection was not attained, a plastic operation was performed in May 1949, in order to create better drainage for the misplaced urethra. She was also operated upon for a pilonidal cyst in 1949, following which considerable time elapsed before complete healing occurred. In 1948 her diabetic state was controlled by small doses of insulin. However, during the administration of insulin she had giant, generalized urticaria. She was subsequently desensitized by subcutaneous and intradermal doses of insulin, starting with 1-unit doses and gradually increasing the amount of material injected until she reached a therapeutic dose adequate for maintaining a normal blood sugar level. She has since been free of any allergic manifestation to insulin.

During the period from the latter part of 1949 through 1951 the patient received various forms of therapy in an attempt to see whether her ketosteroid excretion could be diminished by adequate steroid hormone administration, followed, in turn, by improvement in her clinical picture. A summary of the drugs used and the resultant ketosteroid excretion is presented in Table 1. Prior to the onset of therapy it was noted that she had a ketosteroid excretion ranging between 40 and 80 mg. per twenty-four hours. Therapy consisted of the following: Progesterone was started in December 1949, and was given as an aqueous suspension in doses of 100 mg. three times a week for four weeks. After the failure of progesterone to produce any noteworthy changes and after a suitable control period, she was then given 20 mg. of estrone sulfate, conjugated (Premarin), per day for eight months—from March 1950 until November 1950, with an omission for three weeks from May 21 to June 4. During estrogen therapy there was a tendency for the ketosteroid excretion to be moderately depressed, from a mean of 62 mg. to 44.3 mg. per twenty-four hours (Table 1). However, following discontinuance of the estrogen from November 10 to December 17, 1950, her ketosteroid values returned to their original high levels, ranging from 60.5 to 82.4 mg. per twenty-four hours. Starting on December 17, 1950 the patient was given 40 mg. of Premarin a day until February 1, 1951. During this period of estrogen therapy, little, if any, effect of the estrogen in decreasing the 17-ketosteroid excretion was noted. Following the cessation of estrogen therapy in February, no further medication was given until April 1951. From April 17 to June 7, 1951 the patient received 7.5 mg. of Premarin per day. No depression of 17-ketosteroid excretion was noted. After a two-week control period the patient was given 300 mg. of *p*-hydroxypropiophenone per day, administered for four weeks in order to determine whether this so-called pituitary inhibitor (18–19) would decrease the ACTH output from the hypophysis. No appreciable change in ketosteroid excretion was noted. The dose of this latter drug was increased to 600 mg. per day for three months until October 1951. At no time during the period of *p*-hydroxypropiophenone therapy was there any evidence of alteration of, or decrease in ketosteroid excretion, compared with the values observed during the control period. During this phase of therapy no change was noted in the hypertrichosis or in the amount of insulin required to control the diabetes.

After the cessation of *p*-hydroxypropiophenone therapy the patient was studied for a control period of several weeks, during which time it was noted that her ketosteroid ex-

TABLE 1. EFFECT OF DIFFERENT ENDOCRINE PREPARATIONS UPON 17-KETOSTEROID EXCRETION IN A PATIENT WITH ADRENOGENITAL SYNDROME

Treatment and dose	Duration	No. of determinations	17-Ketosteroid excretion (mg./24 hrs.)		
			Average	Range	
				Low	High
Control	4 wks.	3	42.3	40	44.6
Progesterone, aqueous suspension, 100 mg., 3×wk.	4 wks.	4	44	38	54.8
Control	12 wks.	4	62	58.8	70.5
Premarin, 20 mg. daily (orally)	9 mos.	13	44.3	27.3	82.4
Premarin, 40 mg. daily (orally)	6 wks.	3	60.1	39.8	73.8
Control	10 wks.	2	83.1	76.1	90.3
p-Hydroxypropiophenone, 300 mg. daily (orally)	4 wks.	1	87.2	—	—
p-Hydroxypropiophenone, 600 mg. daily (orally)	3 mos.	2	71.4	71.3	71.5
Control	3 wks.	3	74.1	71.3	79.8
Cortisone, 100 mg. daily (i.m.)	12 days	1	9.9	—	—
Cortisone, 50 mg., as 25 mg. b.i.d. (orally)	1 wk.	1	8.9	—	—
Cortisone, 25 mg., as 12.5 mg. b.i.d. (orally)	5 wks.	4	9.0	7.0	10.0
Cortisone, 12.5 mg. daily (orally)	2 wks.	2	19.1	11.2	27.0
Cortisone, 25 mg., as 12.5 mg. b.i.d. (orally)	5 wks.	4	15.5	14.3	18.0
Cortisone, 37.5 mg., as 12.5 mg. t.i.d. (orally)	2 wks.	2	12.5	12.4	12.5
Cortisone, 25 mg., as 12.5 mg. b.i.d. (orally)	6 wks.	4	16.2	10.2	22.5
Cortisone, 37.5 mg., as 12.5 mg. t.i.d. (orally)	1 wk.	1	5.9	—	—
Cortisone, 25 mg., as 12.5 mg. b.i.d. (orally)	8 wks.	7	16.9	11.4	23.3
Cortisone, 37.5 mg., as 12.5 mg. t.i.d. (orally)	9 wks.	7	10.0	5.5	12.7

cretion ranged between 70 and 90 mg. per day. Following this control period the patient received intramuscular injections of 100 mg. of cortisone per day for twelve days. The data on ketosteroid excretion preceding and during cortisone administration are presented graphically in Figure 1. During the period of intramuscular cortisone administration her ketosteroid excretion dropped from the last control reading of 79.8 mg. to a level of 8–10 mg. per day. At the end of the twelve days of intramuscular therapy the patient

was given 50 mg. of cortisone,[2] administered orally in the form of a 25-mg. tablet twice a day for seven days, from November 19 to November 26. During this period of cortisone administration her ketosteroid excretion stayed below 12 mg. per twenty-four hours. At the end of one week of 50 mg. of cortisone per day, the patient was then maintained on 25 mg. of cortisone daily for several weeks from November 27 through December 30, during which time her ketosteroid excretion ranged between 10 and 11 mg. per twenty-four hours, with an average of about 10 mg. On December 30 the dose of cortisone was decreased to 12.5 mg. a day, but was soon increased to 25 mg. a day on January 12 after her ketosteroid excretion increased to 27 mg. per twenty-four hours while taking the smaller dose. The daily dose of 25 mg. of cortisone was maintained until February 7, when it was increased to 37.5 mg., given in divided doses of 12.5 mg. three times daily

EFFECT OF CORTISONE ON 17 KETOSTEROID EXCRETION OF A PATIENT WITH ADRENAL GENITAL SYNDROME.

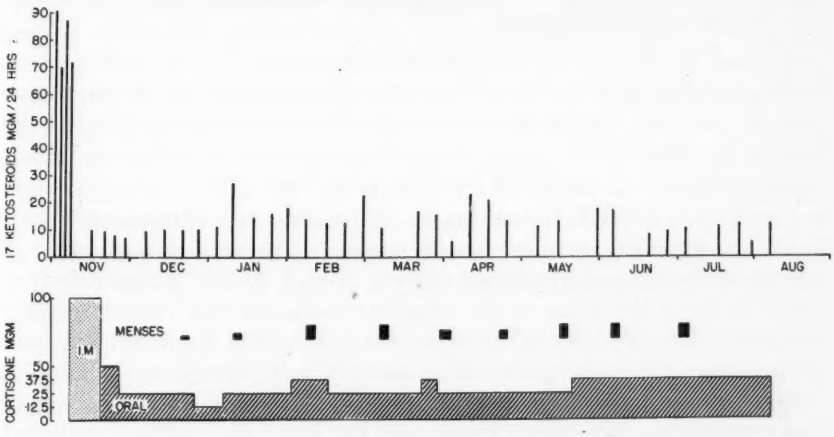

FIGURE 1

for two weeks, in an attempt to determine the relationship between cortisone administration and ketosteroid excretion more accurately. During this period of therapy her ketosteroid excretion decreased to a low level of 12.5 mg. per twenty-four hours. At the end of the two weeks on 37.5 mg. of cortisone daily the patient was again given 25 mg. daily, and was maintained on this dose until March 27, when for one week she was given 37.5 mg. in divided doses of 12.5 mg. three times a day. After one week of therapy her ketosteroid excretion reached its lowest level of 5.9 mg. per twenty-four hours. Following this low reading the dose of cortisone was reduced to 25 mg. a day for eight weeks until June 5, when the patient was once more given 37.5 mg. per day and has since been maintained on this dose. The dose of cortisone was increased and maintained at this level be-

[2] Kindly supplied as Cortogen by Dr. Norman Heminway, Division of Clinical Research of the Schering Corporation.

cause it was previously found that this dose maintained her ketosteroid excretion below 12–13 mg. per twenty-four hours. It was anticipated that such a depression of 17–ketosteroid secretion would enhance the elaboration of endogenous estrogenic substances. During the entire phase of cortisone ingestion, covering a period of eight months of administration, it was noted that the patient had experienced nine spontaneous menstrual periods, more or less regularly spaced (Fig. 1). It is to be emphasized that at no time during the period of cortisone administration had the patient received any cyclic therapy with estrogen or progesterone. In addition to the remarkable effect of cortisone in suppressing the patient's 17-ketosteroid excretion, the glycogenic steroid produced marked alteration in the patient's insulin requirements. During the period of cortisone administration her fasting blood glucose values increased to 170 mg. per 100 cc. Her dose of insulin had to be increased and regulated fairly carefully, inasmuch as there was marked variation in the level of both urinary and blood glucose. Although in the early period of corticosteroid intake the patient noted some increase in breast size, there had been little change in this respect for several months. There had been no detectable alteration in the hypertrichosis in the early part of the study. After receiving therapy for nine months a decrease in hirsutism was observed.

DISCUSSION

The mechanism of action of cortisone in decreasing the patient's ketosteroid excretion, associated with reinstitution of menstrual periods, can well be ascribed to the action of the 11-oxysteroids in depressing adrenal cortical activity, as suggested by Wilkins (10–14). This involves primarily a suppression of ACTH secretion by the exogenously administered cortisone, accompanied by a decrease in adrenal corticoid secretion, predominantly of the sex and glycogenic steroids (10–14, 20–22). Apparently there must be little alteration in the electrolyte-maintaining steroid secretion from the adrenal cortex of these patients, since data from animal experiments suggest that these steroids are not under the direct control of pituitary ACTH activity (23–25). While the secretions of the glycogenic steroids are suppressed, the metabolic need of the body for such compounds is adequately supplied by the exogenous preparation.

The only concrete evidence of suppression of adrenal cortical activity following the administration of cortisone is depicted by the marked alteration in 17-ketosteroid excretion. Such a change implies physiologic suppression by cortisone of endogenous cortical steroids of predominantly the androgenic group. This in turn, results in a more normal secretion and release of enough pituitary gonadotropic hormone for normal ovarian stimulation. During the active phase of the adrenogenital syndrome, prior to cortisone administration, there are apparently sufficient 17-ketosteroid precursors being elaborated from the adrenal cortex to suppress effectively the normal gonadotropic secretion from the patient's anterior hypophysis. Inhibition of such excessive steroid production by the adrenal cortex, through the use of cortisone, results in a release of gonadotropic hormone and enables the resumption of normal cyclic ovarian activity. Menstrual

periods soon occur due to the physiologic stimulation of the endometrium of the patient by the increased elaboration of endogenous ovarian hormones.

The amount of oral cortisone therapy necessary for controlling the adrenogenital syndrome can be determined fairly accurately by evaluating the patient's 17-ketosteroid excretion. In our study it was noted that a total daily dose of 37.5 mg. of cortisone administered in divided doses three times a day resulted in 17-ketosteroid excretion values below 13 mg. per day. The suppression of the 17-ketosteroid excretion to this level by cortisone probably represented the true level of ketosteroid precursors from the adrenal cortex. The administered cortisone in the small doses employed accounted for little, if any, of the 17-ketosteroid measured in the 24-hour urine. Somatic changes, manifested only by a limited increase in breast size, were nevertheless accompanied by the resumption of fairly regular menstrual cycles. Although little change in hypertrichosis was noted during the first six-month period of this study, a definite decrease in the extent of the hirsutism was noted after the patient had been maintained on adequate cortisone therapy for nine months.

SUMMARY AND CONCLUSIONS

Cortisone initially administered intramuscularly in doses of 100 mg. per day depressed, within one week, the elevated ketosteroid excretion noted in a 37-year-old female patient with a 22-year history of adrenogenital syndrome.

After twelve days of intramuscular cortisone, the patient was maintained for more than eight months on oral cortisone. The dosage for oral administration was ascertained quantitatively by 17-ketosteroid excretion studies. Excretions below 13 mg. per day were maintained by a total daily dose of 37.5 mg. of cortisone administered in divided doses three times daily.

During this regimen the patient showed minimal somatic changes, but experienced nine spontaneous, fairly regular menstrual periods.

The comparatively small dose of cortisone (37.5 mg. per day), although adequately depressing the patient's ketosteroid excretion, adversely affected her mild diabetic state and made its control with insulin difficult. Before cortisone therapy, massive doses of estrogen, progesterone, and *p*-hydroxypropiophenone had failed to produce significant changes with respect to her amenorrhea or ketosteroid excretion.

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ARTHRITIS AND PANHYPOPITUITARISM

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THE occurrence of arthritis in Simmonds' disease has been mentioned many times but never as a characteristic feature (1). However, Sheehan observed that patients with hypopituitarism were "unduly liable to develop rheumatism in the knees" (2). Gallavan and Steegman hinted that the arthritis might be associated with a secondary involvement of other endocrine glands rather than with the pituitary insufficiency (3). It is the purpose of this paper to emphasize the finding of arthritis in hypopituitarism as significant and to suggest a relationship between the two conditions on a pituitary basis in the light of newer theoretical concepts.

REVIEW OF THE LITERATURE

The clinical picture of anterior pituitary insufficiency resulting from a destructive disease of the anterior lobe of the pituitary was first described by Simmonds (4). Sheehan showed that the most common cause is postpartum necrosis of the anterior pituitary, due to hemorrhage-collapse at the time of delivery, and his name has since been attached to the syndrome of hypopituitarism having this etiology (5, 6).

In the cases in which arthritis was present, the onset of arthritic symptoms occurred six months to twenty-eight years after the significant delivery and the average age at onset was 37 years (3, 7–15). One or more major joints were involved in every case but the knees were affected most frequently. Clinically, the patients had the usual joint complaints of pain, swelling, stiffness and deformities. A definite diagnosis of the type of arthritis was not made except in a patient reported by Cook *et al.* who had rheumatoid arthritis (9). The ensuing cases are the second and third reported as having rheumatoid arthritis associated with Sheehan's syndrome.

CASE REPORTS

Case 1

Mrs. A. B. W. was a colored female, aged 28. She was seen in August 1950, complaining of swelling, tenderness and excruciating pain on motion in all major joints. Her health and menses had been normal until the age of 21, when her only pregnancy occurred. She had a very difficult delivery of twins, accompanied by severe blood loss. The first baby

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was born after eighteen hours of labor, and was followed by a stillborn baby twenty-four hours later. The patient did not lactate and her menses did not return. Some time later she noticed that she could not stand the cold and had to have blankets around her to keep warm, even in summer. Her genitalia and breasts became small, libido was lost, axillary and pubic hair fell out, and the cephalic hair became coarse and thin. Two years after delivery she had fever with pain and swelling in the small joints of her hands; this disappeared after a short time but frequently recurred. Other joints were similarly involved as this process continued, and deformities resulted. Spots of white appeared on her skin after several years and these gradually increased in size and number.

On examination, the patient was an emaciated colored female who could not walk because of her joint deformities and pain. Her face was wrinkled and she appeared about twenty years older than stated. Her temperature was 100.2° F. and her pulse rate 94/min. She was depressed and slow in speech. The cephalic hair and eyebrows were thin; axillary and pubic hair were absent. Her knees were swollen, warm and tender; there was fusiform swelling of the proximal interphalangeal joints of the fingers and ulnar deviation bilaterally; the knees, elbows, and fingers had flexion deformities and the muscles about the joints were atrophied, exaggerating the joint swelling. The breasts and genitalia were atrophic. Her skin was dry and was speckled diffusely with spots of white, about 0.5 cm. in diameter. The rest of the examination and routine laboratory studies gave normal findings.

The diagnoses were: acute exacerbation of rheumatoid arthritis and Sheehan's syndrome (severe).

Case 2

Mrs. E. I. was a white female, aged 36. She was seen in March 1951, complaining of pain in the joints. She was a gravida II para I, whose health and menses had been normal until her first pregnancy at the age of 22. After thirty-four hours of difficult labor, accompanied by severe blood loss, she delivered a normal infant. She did not lactate. Her periods returned three months post partum but the flow was not as heavy as before. Nine months after delivery she had a ruptured tubal pregnancy and apparently was in profound shock. After recovery, her periods did not return and libido was lost. There was a decrease in energy and she was unable to do her housework. The axillary hair gradually fell out; the cephalic hair became coarse, dry and thin; and the eyebrows became thin. She noticed a craving for sweets and had at least one authenticated hypoglycemic crisis. A marked cold intolerance gradually developed, and about seven years post partum she showed myxedema, which responded well to treatment with thyroid. In October 1950, the small joints of her left hand first became tender, red, swollen and painful on movement. These symptoms subsided after a short time but recurred frequently and involved the knees, ankles and wrists.

On examination, the pertinent findings were: temperature 99.6° F.; pulse rate 90/min.; the cephalic hair was thin, dry and coarse; the eyebrows were thin; the pubic hair was sparse; her skin had a waxy pallor and her cheeks and lips were pale; the breasts were small; the vagina and uterus were almost atrophic; and the ankles and small joints of her hands were reddish, warm, tender and swollen. Motion was limited in these joints, particularly in the fingers, and there was some early fusiform swelling of the proximal interphalangeal joints of the fingers. Routine laboratory findings were normal, except for a sedimentation rate of 30 mm./hour.

The diagnoses were: acute rheumatoid arthritis and Sheehan's syndrome (moderate).

DISCUSSION

The incidence of arthritis and rheumatism in this country is about 5.9 per cent, which is about the same as elsewhere (16). Sheehan noted joint disease in 13 of 96 cases of pituitary necrosis, which is an incidence of 13.5 per cent (17). Therefore the incidence of arthritis in hypopituitarism appears to be more than twice as high as would be expected in a random group of the general population. The reason for this is unknown, but the following is suggested as a possible facet of its explanation.

Sheehan's syndrome may be considered as a disease of hypoadaptation. It has been shown experimentally that when hypoadaptive animals are exposed to new nonspecific stress, they may show new lesions of other diseases, one of which is arthritis (18, 19). Since patients with hypopituitarism have a partial loss of pituitary, they are hypoadaptive and would be expected to contract other diseases when exposed to new stress. Accordingly, arthritis may occur at any time in these patients.

SUMMARY

Arthritis occurring in hypopituitarism has received little attention in the literature. Two cases of rheumatoid arthritis associated with hypopituitarism are presented, making a total of 3 reported cases in which the two conditions were diagnosed concomitantly.

The incidence of arthritis in patients with hypopituitarism appears to be more than twice that found in the general population, indicating that arthritis is a significant and not an uncommon finding in these patients. A possible explanation is suggested on the basis of their hypoadaptive condition.

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LETTERS TO THE EDITOR

EFFECT OF TETRAETHYLAMMONIUM BROMIDE ON THE EOSINOPENIC RESPONSE TO EPINEPHRINE

To the Editor:

Until recently, the eosinopenic response to epinephrine was used as a test for the integrity of the pituitary-adrenocortical system. Serious doubt about its validity as a test has been aroused lately (1, 2), because the eosinopenic response to epinephrine has been observed in human subjects who have undergone bilateral adrenalectomy, indicating that the presence of the adrenal cortex is not always necessary for the response.

The following investigation upon the effect of the autonomic nervous system on the eosinopenic response to epinephrine may be of interest, compared to the more recent considerations:

Material and methods: In the first group were 15 subjects proved by different clinical and laboratory investigations to present no endocrine disorders. All were subjected to sufficient bed rest and observation. Fasting counts of eosinophil cells in peripheral blood were performed before, and four hours after, the subcutaneous injection of 0.3 mg. of epinephrine, as described by Recant *et al.* (3). Epinephrine injection was repeated the following day under the same conditions, one hour after the intravenous injection of 20 mg. of tetraethylammonium bromide (TEAB). Blood pressure was recorded before and after administration. Except for a slight tinnitus occurring in nearly all the patients, no noteworthy reactions, such as shock or collapse, were noted after the intravenous injection of TEAB.

In the second group 6 subjects were given 25 mg. of ACTH intramuscularly, and their eosinopenic responses were recorded in the manner described by Recant *et al.* The next day the same test with ACTH was repeated, following 20 mg. of TEAB injected intravenously.

Results: The results obtained are shown in Figures 1 and 2. It may be seen that 14 subjects out of 15 responded normally to the epinephrine injection, and presented an eosinopenic response ranging between −55 per cent and −80 per cent. The results obtained after the injection of TEAB were remarkable. In all but 1 case (in which ganglion blockade was produced by TEAB) there was an abnormal eosinopenic response to epinephrine, and in 4 cases there was an inverse response (Fig. 1). Similar

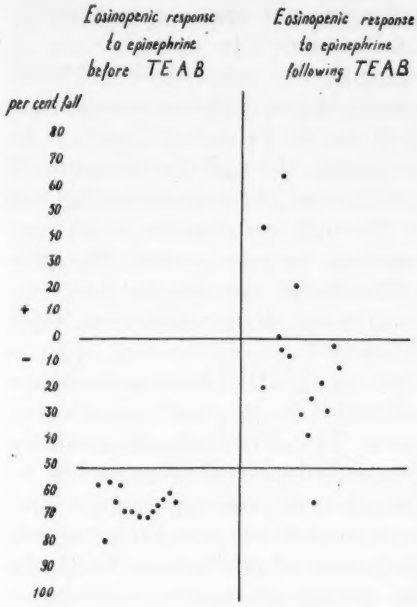

FIGURE 1

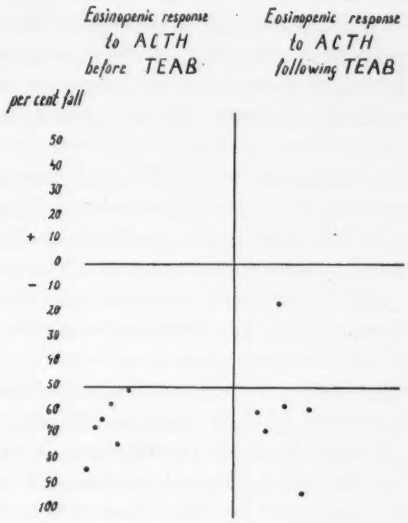

FIGURE 2

changes noted in nearly all our experiments show that TEAB possesses a notable effect on the eosinophil count.

The eosinopenic response to ACTH was, as expected, in normal cases between −50 per cent and −85 per cent, and was not affected by TEAB blockade. Thus, the eosinopenic response to ACTH is not affected by TEAB previously injected.

Discussion: It has been shown that adrenergic blocking agents (such as dibenamine) prevent the alarm reaction caused by adrenalin. It has been pointed out that they do not prevent the effects of stressors other than adrenalin (4). On the other hand, Fritz and Levine have demonstrated that in adrenalectomized animals dibenamine does prevent the action of stressors other than adrenalin (such as formalin and cold (5, 6)). Thus, according to these authors, dibenamine is not limited to preventing the stressor action of epinephrine only.

We have used in our investigations, tetraethylammonium bromide, which has a blocking effect on the synapses of sympathetic and parasympathetic nervous system ganglions, by interrupting or inhibiting cholinergic transmission. The mechanism of the action of epinephrine in epinephrine-induced eosinopenia is not clearly understood. That epinephrine acts by liberation of ACTH is uncertain and is not indicated by the results

obtained in these experiments. That epinephrine occasions eosinopenia directly through some unknown mechanism cannot be upheld, since its action should not be prevented by the ganglion blockade caused by TEAB. Thus, the autonomic nervous system seems to play a part in epinephrine-induced eosinopenia. Indeed, as pointed out by Fritz and Levine, "the action of stressors takes place, at least partly, through the mediation of sympathomimetic agents." According to Levine, the response of the central nervous system to stressors occurs through two principal channels—the liberation of ACTH, and the autonomic nervous system. The anti-stressor actions of substances such as dibenamine, atropine and banthine, which have a blocking effect on the autonomic effector agents or which prevent their formation, favor this point of view.

TEAB has been found to have no effect on ACTH-induced eosinopenia, showing that the eosinopenic action of ACTH is completely independent of the nervous system, as already known. That TEAB should block the eosinopenic response to epinephrine but should have no effect on the response to ACTH, leads to the idea that all eosinopenic agents do not act through the same mechanism. It thus seems possible that there may be, besides the hormonal mechanism, other ways of producing eosinopenia, as suggested by the observation that epinephrine-induced eosinopenia may be suppressed or reduced through the use of ganglion-blocking agents.

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CONVERSION OF CORTISONE TO COMPOUND F

TO THE EDITOR:

In this *Journal* Burton, Keutmann, and Waterhouse (1) published data concerning excretion of corticosteroids in patients treated with cortisone. They concluded that cortisone is convertible into compound F in the human body and that an extra-adrenal mechanism is the most important one.

In enzymatic studies we have confirmed these findings (2). After the incubation of cortisone with liver homogenates of rat, pork, and beef we demonstrated the presence of 17-hydroxycorticosterone (compound F) on paper chromatograms. The activity of rat liver in transforming cortisone to compound F varied from 10 to 80 per cent of the incubated cortisone; beef adrenals showed considerably less activity; rat kidneys and muscles gave negative results.

The highest activity was in whole liver homogenates. After a differential centrifugation procedure microsomes, not mitochondria, were most active, whereas the supernatant fraction obtained at 105400×g demonstrated no activity. These data indicate that the enzyme system is associated with the structural elements of the liver cells.

Diphosphopyridine nucleotide, ascorbic acid, citric acid, and oxygen stimulated the conversion. As_2O_3, NaCN, and nitrogen had the reverse effect.

Methods: Portions of the homogenate in amounts equivalent to 200 mg. of original tissue were incubated at 37° C. for four hours in 4 ml. of phosphate buffer (pH 7.3) containing 100 micrograms of cortisone. After incubation the mixture was extracted with chloroform, the chloroform evaporated, and the steroids followed by use of the Zaffaroni procedure (3). For the identification of the products we used various fluorescent and reducing reactions, the R_f values, and UV-spectrometric methods. For quantitative measurement we located the steroids by contact photography in ultraviolet light, and after elution with ethanol we determined their optical density in a Beckman spectrophotometer (model DU), as reported elsewhere (4, 5, 6).

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GYNECOMASTIA AND HYPERTHYROIDISM

TO THE EDITOR:

In a recent communication to this *Journal*, Bauer and Goodwin (1) reported 3 cases of gynecomastia appearing in patients treated with radioactive iodine for Graves' disease. This symptom was considered as a complication of such therapy.

We wish to call attention to tender breast enlargement as one manifestation of the symptomatology of Graves' disease itself and to present 4 such cases in males observed in the past one and a half years among a total of 45 cases of hyperthyroidism examined during this period. In 2 of the cases, the appearance of breast symptoms antedated therapy of any kind. In 1 case, gynecomastia was first noted shortly after institution of therapy with Tapazole (1 methyl 2 mercaptoimidazole) but before significant clinical response was evident. In the fourth case, tender breast swelling was first noted later in the course of therapy, at a time when the patient had improved considerably. In all cases, remission of breast symptoms coincided with the return of function to the euthyroid state.

CASE REPORTS

1. *J. F.*, a 31-year-old white man, was admitted June 18, 1951, with weight loss of 30 pounds, tremor, exophthalmos, and heat intolerance. Physical examination revealed a profusely sweating young man with a tachycardia of 120, exophthalmos, and a diffusely enlarged thyroid. The BMR was +64 per cent, the thyroidal I^{131} plasma clearance (2) was 229 ml./min., and the 24-hour thyroidal uptake of I^{131} was 75 per cent. On admission the patient was started on Tapazole therapy, 5–10 mg. every six hours. On August 17 he

complained of mild pain in both breasts and hypertrophy of the breasts was noted for the first time. At this point the patient's symptoms had not completely subsided and the BMR was +46 per cent. On October 3 thyroidectomy was performed; the thyroid tissue which was removed weighed 58 grams. On October 15, 1951, his BMR was +2 per cent and gynecomastia was no longer present.

2. *W. J.*, a 27-year-old white man, was admitted November 14, 1951, with a 50-pound weight loss, tremor, nervousness, diarrhea and palpitation of the heart. The patient appeared emaciated, the pulse was 116/min., tremor and sweating were marked, and the thyroid was diffusely enlarged. The thyroidal I^{131} plasma clearance was 291 ml./min. The BMR, obtained three weeks before admission, was +62 per cent. Tapazole was started on November 14 in a dosage of 5 mg. every six hours, which was increased to 7½ mg. on January 18, 1952, because of persistence of symptoms and elevated BMR (+34 per cent). More rapid improvement ensued, and on February 25 the BMR was 0. On this date the patient complained of right breast tenderness and hypertrophy of both breasts was noted. On March 7 thyroidectomy was performed; the thyroid tissue which was removed weighed 64 grams. On March 25, 1952, the patient was discharged, symptom-free without gynecomastia.

3. *R. L.*, a 24-year-old white man, was admitted September 16, 1952, with recurrent episodes of weight loss, tremor and nervousness and painful swelling of both breasts, of six months' duration. The pulse was 100, the thyroid was diffusely enlarged, and the skin was moist and warm. The breasts were tender and hypertrophied bilaterally. The BMR was +41 per cent, the 24-hour thyroidal uptake of I^{131} was 90 per cent, and the thyroidal I^{131} plasma clearance was 373 ml./min. Tapazole was started on October 2 in a dose of 20 mg. every six hours. On October 14 the BMR was +21 per cent. Clinical improvement was noted by October 15, at which time the breast tenderness had markedly diminished, although some breast swelling was still present. On November 10 the breasts were normal. Thyroidectomy was performed on November 18, and the patient was discharged on December 5, 1952, without symptoms.

4. *A. O.*, a 55-year-old white man, on maintenance digitalis for rheumatic heart disease with auricular fibrillation, was admitted August 19, 1952, with weight loss, sweating, heat intolerance, tremors, and tender enlargement of the right breast. The blood pressure was 190/90, the ventricular rate was 80, and the thyroid was of normal size. Lid lag, fine tremor and moist skin were present. The right breast was enlarged and tender. There was enlargement of the heart with diastolic murmurs of the apex and base. On August 27 the thyroidal I^{131} plasma clearance was 125 ml./min., with a 24-hour thyroidal uptake of 80 per cent. On September 3 he received a therapeutic dose of 4.5 millicuries of I^{131}, following which he was maintained on Tapazole in doses varying from 5 to 20 milligrams every six hours. On October 30, 1952, the right breast was normal in size and non-tender. The patient was clinically euthyroid.

Although mention of gynecomastia in relation to hyperthyroidism could not be found in Mean's text on thyroid disease (3), sporadic references to this association have appeared in the literature (4–7) since Basedow's original case (8), and McGavack (9) apparently accepts gynecomastia as a not uncommon symptom in Graves' disease. Discussion of the endocrine factors involved in the production of tender breast enlargement in this disorder is beyond the scope of this brief report. However, the relatively high

incidence noted in this small series should stimulate search for the presence of this symptom in all cases of hyperthyroidism.

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ADDITIVE TOXIC EFFECTS OF PHENOBARBITAL AND ITRUMIL

TO THE EDITOR:

In 6 out of 75 patients treated with Itrumil® (Na-5-iodo-2-thiouracil) in doses varying from 200–600 mg. daily and simultaneously receiving phenobarbital in doses of 1 to 4 grains per day, manifestations such as generalized pruritus and maculopapular rash were observed. These reactions appeared usually during the first week of treatment. In all cases, the toxic manifestations were eliminated when the phenobarbital was discontinued. The discontinuance of Itrumil did not cause the toxic reactions to disappear. In 1 case, when phenobarbital was readministered, the toxic signs re-appeared. Four of the cases are summarized as follows:

S. M., a 42-year-old female with acute hyperthyroidism, had been treated previously with methylthiouracil (200–400 mg. daily) and phenobarbital (3 grains daily) without any toxic reactions. On the seventh day of treatment with Itrumil (200 mg. daily) and phenobarbital (3 grains daily), a scattered pustular-papular rash on face, arms, legs and chest was noted, together with marked pruritus. Itrumil was discontinued but the toxic manifestations persisted with equal intensity until the phenobarbital was discontinued. When phenobarbital was readministered, the rash and pruritus re-appeared.

R. L., a 34-year-old female with acute hyperthyroidism, receiving phenobarbital (2 grains daily) prior to antithyroid medication without toxic reaction, was prepared initially for surgery with Itrumil (400 mg. daily) and phenobarbital (2 grains daily). On the

fifth day of treatment a generalized pruritus was noted. Phenobarbital was discontinued and the pruritus disappeared. The patient continued on Itrumil for four weeks without any further toxic manifestations. Therapy with I^{131} was given afterwards.

E. O., a 54-year-old female with acute hyperthyroidism, receiving phenobarbital (1½ grains daily) prior to antithyroid medication without toxic manifestations, was given preoperatively Itrumil (200–400 mg. daily) and phenobarbital (3 grains daily). On the fifth day of treatment a generalized macular rash and pruritus were observed. These toxic manifestations disappeared after phenobarbital was discontinued. The patient was continued on Itrumil for two weeks, until operated on, without further toxic reactions.

W. J., a 47-year-old female with acute hyperthyroidism, receiving phenobarbital (2 grains daily) without toxic reactions, was prepared for surgery with Itrumil (400 mg. daily) and phenobarbital (1½ grains daily). On the fourth day of treatment generalized pruritus appeared and was controlled when phenobarbital was discontinued. Itrumil was continued for four weeks, until the patient was operated on, without any further toxic reactions.

The additive toxic effect of phenobarbital and Itrumil can be explained by the fact that both compounds have a pyrimidine structure. There is no literature to substantiate this theory.

This report suggests that certain toxic manifestations often attributed to the use of thiourea derivatives may be due to the phenobarbital simultaneously administered.

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ASSOCIATED PARATHYROID AND PITUITARY (CHROMOPHOBE) ADENOMAS: PERSISTING HYPOPHOSPHATEMIA AFTER THE CURE OF THE HYPERPARATHYROIDISM

TO THE EDITOR:

Underdahl and co-workers (1), commenting on our paper with the above title (2), say that we fail to admit the possibility of another parathyroid tumor besides the one removed, as the probable explanation for the persisting hypophosphatemia. Such an hypothesis was not discussed because it had been ruled out by the data reported: (a) according to the case record, "the exploration of the parathyroid glands showed one adenoma, which was removed"; only one adenoma was found. Moreover: (b) the patient had hypercalciuria before the removal of the parathyroid tumor (average daily urinary calcium, 402, 355 and 389 mg. in three metabolic periods, while the diet contained 180 mg.), in contrast with normal excre-

tion (187 and 187 mg. in two periods, on the same diet) two years after the parathyroid operation, when the patient was readmitted and still showed low serum phosphate levels (2.0 and 2.8 mg. per 100 ml.).

The striking feature of the case was the lack of a lasting rise in the blood phosphate level after the excision of the parathyroid tumor. During three months, beginning one week after the operation, the following values for serum phosphate were obtained: 2.6, 2.8, 2.9, 3.6, 2.7, 3.1, 3.0, 2.8, 2.9 and 3.0 mg. per 100 ml.; the results of successive determinations in the three months prior to the operation had been: 2.5, 2.8, 2.7, 2.5, 2.0, 2.5, 2.0, 2.6 and 4.3 mg. per 100 ml. Paralleling the phosphate curve, serum calcium values in the postoperative period were 9.5, 10.0, 9.8, 11.0, 10.2, 10.2, 10.4, 10.3 and 10.3 mg. per 100 ml.; the absence of hypocalcemia may be explained by the failure of a rapid bone remineralization to take place, and this may be due to the lack of a significant postoperative increase in the phosphate concentration. From our standpoint in this discussion, the time factor should be given particular importance. A hyperphosphatemia did develop in the twenty-four hours following parathyroid tumor removal, when the value of 7.0 mg. per 100 ml. was reached; the inability of the organism to maintain the hyperphosphatemia, as is usual in such a postoperative period, points to the existence of some peculiar defect in the phosphate metabolism. In view of the existence of a pituitary lesion in the case (chromophobe adenoma) we suggested that the abnormality of phosphate metabolism might be due to some pituitary insufficiency (growth hormone?) besides the insufficiency of the gonadotropic function (amenorrhea, with less than 7 m.u. of urinary gonadotropins per twenty-four hours).

Interestingly enough, the adrenocorticotropic function was normal; normal results were obtained with every adrenal function test performed (urinary 17-ketosteroids, ACTH eosinopenia, insulin and glucose tolerances, and Robinson-Power-Kepler test). Would this normal adrenocortical function be a condition for the hypophosphatemia, since a low serum phosphate level is not a feature of cases of panhypopituitarism?

Of course we would fail in any attempt to explain how the adenoma could dissect the pituitary functions in such way. The whole hypothesis may be disregarded. We only wish to insist on the facts observed, chiefly because they concern the interesting and still poorly understood picture of multiple endocrine adenomata.

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Teaching Clinic

AN UNUSUAL CASE OF MALIGNANT EXOPHTHALMOS AND POSTOPERATIVE HYPOTHYROIDISM COMPLICATING GRAVES' DISEASE

THE etiology of Graves' disease is poorly understood at best, and even less is known as to why some cases show certain unusual complications of presumed pituitary origin, such as malignant exophthalmos, whereas others do not. With regard to possible etiologic factors, it is well known that hyperthyroidism is occasionally observed in individuals receiving thyroid therapy for conditions other than hypothyroidism, such as obesity. This sequence of events is not necessarily related to the size of the dose of thyroid. However, although many such cases have been documented, the critical observer will have to agree that there is no proof that thyroid therapy is responsible for the development of hyperthyroidism after discontinuation of treatment. There are no adequate statistical data available to indicate whether the incidence of hyperthyroidism among individuals who have previously received thyroid hormone is significantly greater than that in the population at large. Nevertheless, students of this subject are in agreement that, until proven otherwise, injudicious use of desiccated thyroid must be considered as a possible etiologic factor in Graves' disease. This possibility should temper the use of this hormone in conditions other than that for which there is a clear indication, *i.e.*, hypothyroidism.

The case under consideration is being presented as an example of possible iatrogenic Graves' disease, with unusual complications. It illustrates some of the complexities in both interpretation and management of some patients with thyroid disease.

The patient (D.H. unit No. C-57467), a 41-year-old white married woman, was first seen by the Ophthalmologic Service at Duke Hospital on March 28, 1949, because of progressive exophthalmos and loss of vision of eight to nine months' duration. Her present illness began in August 1947, prior to which date she had been in good health. At that time she began to complain of vague left anterior thoracic pain, weakness and fatigue; thyroid medication was prescribed in a dose of 60 mg. per day, with apparent relief of symptoms. Approximately nine months later she became aware of the insidious onset of tachycardia, palpitation, mild tremor of the hands, increased nervousness and emotional lability, heat intolerance, hyperhydrosis and weight loss, and her menses became scanty and irregular. Two months later she noted puffiness of her cheeks and eyelids and a BMR was recorded as +36 per cent. Thyroid medication was discontinued and

treatment with Lugol's solution and propylthiouracil begun. There was some improvement in symptoms during the subsequent two months, but progressive swelling of the eyelids, protrusion of the eyeballs and loss of vision, particularly related to color perception, now developed. Despite these latter symptoms, a thyroidectomy was performed in November 1948. After this procedure, vision was further markedly reduced and there occurred in addition marked embarrassment of extraocular movements, the patient being unable to look to the right or left. Postoperatively, there was a gradual subsidence of the symptoms of hyperthyroidism and weight was slowly regained, but the eye symptoms not only were unimproved, but showed further progression. During the four months prior to admission, she noted the gradual development of mental sluggishness, cold intolerance, hoarseness and anhydrosis, and her menses became regular and profuse.

The important physical findings related particularly to the skin and its appendages, and the eyes. Her temperature was 37°C, pulse 80, and blood pressure 120/80 mm. No thyroid tissue was palpable. The skin was glistening, smooth, slick, dry and fairly thick. The hair was definitely dry, but not unduly coarse. The face lacked expression. There was marked exophthalmos, measuring 27 mm. in both eyes, with striking soft swelling of both upper and lower lids (Fig. 1), but no chemosis. Vision was limited to counting fingers with the right eye and to 20/400 in the left eye. Extraocular movements were limited, particularly in the left eye, which could not be deviated laterally. The corneae were clear, and the pupils were round, regular and equal and reacted to light and accommodation. Funduscopic examination revealed a residual edema in and about each disc. Cooperation was so difficult that visual field examination was considered unreliable. There was probably a caecocentral scotoma on the right and a central scotoma on the left. There was constriction of both peripheral fields. The ophthalmologist thought that the visual disturbances represented a retrobulbar neuritis. A point of interest was the persistent loss of color vision, far out of proportion to that which would be anticipated with the degree of visual acuity.

Laboratory studies revealed normal hemogram and urinary findings. BMR's were −17 per cent and −32 per cent. The concentration of serum total protein was 7.7 Gm., albumin 5.1 Gm., globulin 2.0 Gm., and cholesterol 230 mg. per 100 cc. X-ray examination of the chest, skull, and orbits showed nothing abnormal.

The patient was discharged on April 2, 1949, to the care of her local physician with the recommendation that she receive radiotherapy to the pituitary, and desiccated thyroid by mouth. Radiotherapy was administered in June 1949, but the advice to administer thyroid was not followed. On July 13, 1949, she was seen by the Ophthalmologic Service again. Vision in the right eye had deteriorated further, whereas that in the left had improved to 20/60. The exophthalmos was unchanged. Orbital decompression was considered but deferred, pending further observation.

She next returned on October 5, 1949, and was seen for the first time by the present observer. Some improvement in vision was reported by the patient. Her chief new complaint was the development of a peculiar hard swelling of both hands, lower legs and feet. This was non-pitting and non-painful and was so hard as to suggest bone, but x-ray examination by her local physician revealed no bony involvement or calcification of the subcutaneous tissues. Mental slowing, sluggishness, dryness of the skin and hair, decreased sweating, cold intolerance and menorrhagia had now become more prominent.

On physical examination, some improvement in vision and a definite decrease in edema of the lids were noted, but the degree of exophthalmos was unchanged. Extraocular movements were normal. Both optic discs were somewhat pale. Visual field constriction was less. The face as a whole was puffy and lacked expression (Fig. 1). The skin had

FIG. 1. Appearance of facies and eyes of patient prior to present illness (1938), five months after thyroidectomy (3-28-49), twelve months after thyroidectomy (10-5-49), and after ten months of thyroid therapy (8-9-50).

a pasty yellowish cast, was dry and fairly smooth. There was an extraordinary firm, non-tender, non-pitting edema involving the fingers and dorsum of the hands, the shins and the feet. The skin over the shins was shiny and fixed; it had a pigskin appearance, but none of the characteristic elevated lesions of myxedema circumscripta (Fig. 2). There was some curvature of the nails and suggestive early clubbing (Fig. 3). For the first time, the deep tendon reflexes were noted to exhibit the slow relaxation that is char-

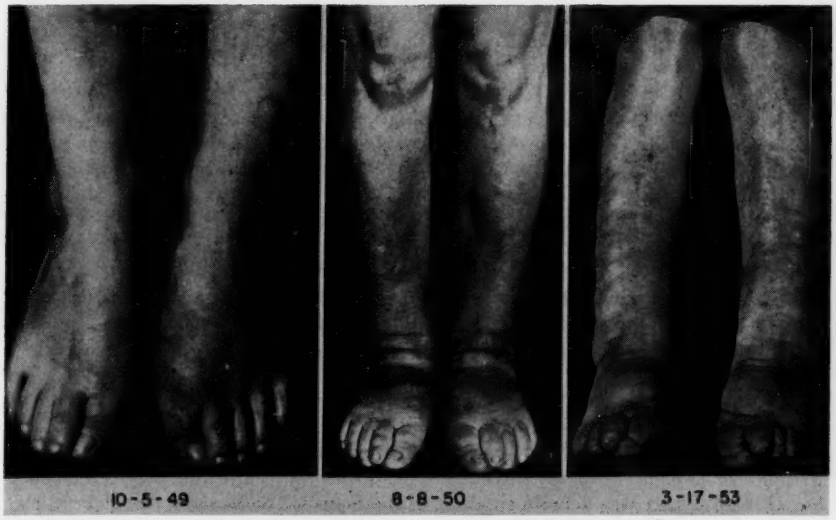

FIG. 2. Stages in the progressive development of localized myxedema of the lower legs

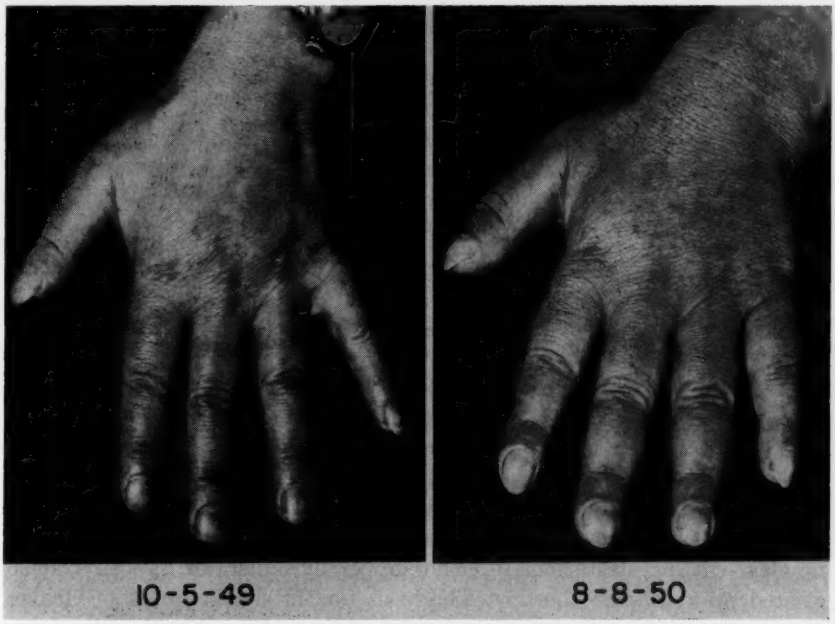

FIG. 3. Localized myxedema of hands and clubbing of fingers.

acteristic of myxedema. The BMR was −15 per cent. The serum cholesterol level was 365 mg. per 100 cc. Therapy was begun with 30 mg. of desiccated thyroid daily.

The patient was next seen on August 4, 1950.

In the ten-month interim, she had taken thyroid regularly and had shown great improvement with respect to most all symptoms of hypothyroidism, as well as a definite increase in vision and subsidence of orbital and lid edema, but there had been marked progression of the hard brawny swelling of the hands and feet. The latter had occurred despite increasing her dose of thyroid to the limit of tolerance, *i.e.*, 300 mg. daily. The swelling of her feet had increased to such a degree that she had to wear shoes several sizes larger than before. She also had noted the development of "tender knots" and blisters on her shins.

Physical examination showed her temperature to be 37°C, pulse 118, and blood pressure 120/80. Exophthalmos and lid swelling appeared definitely decreased, although exophthalmometric readings were 25 mm. in the right eye and 26 mm. in the left. Vision was now 20/30 O.D. and 20/25 O.S. Funduscopic examination revealed the slight pallor previously described. The patient was definitely more alert and bright. With the exception of her hands, legs and feet, her skin in general was smoother and moist. Deep tendon reflexes were normal. The most striking changes were in the extremities. There was further swelling of hands and fingers, with one very hard area in the right snuff box (Fig. 3). There was definite clubbing of the fingers. The legs and feet showed massive, stony-hard edema which did not pit and which produced gross malformation of the feet (Fig. 2). The skin was thick, tense and fixed, with a pigskin appearance. There were a number of firm, indurated, raised plaques, ranging from a few millimeters to several centimeters in diameter. Several flat irregular bullae occurred in association with the plaques. The areas of abnormal skin and edema extended two-thirds of the way up the legs, with a fairly well demarcated border.

The BMR's were +3 per cent and +4 per cent. The concentration of serum cholesterol was 210 mg., total protein 6.5 Gm., albumin 4.2 Gm. and globulin 2.3 Gm. per 100 cc. The urine was normal.

In the subsequent thirty-four months of observation, there has been progressive improvement in her eyes. Visual acuity is O.D. 20/30 and O.S. 20/25. Visual fields and extraocular movements are normal. The periorbital edema has softened and decreased. Exophthalmos, however, is essentially unchanged, with readings of 26 mm. O.D. and 26.5 mm. O.S. The edema of the hands and legs has been modified little, if any, being even greater when last seen (March 17, 1953) than before (Fig. 2). A period of strict dietary salt restriction (rice diet) from August 10, 1950 to March 8, 1951 resulted in a 6-Kg. weight loss, but no detectable change in the edema. Treatment with ACTH and cortisone for several months likewise was without effect. At present, the patient is on a free diet, taking 150 mg. of desiccated thyroid daily, and is relatively well adjusted psychologically to her deformities.

Comment: There is no way of proving that the use of thyroid by this patient in 1947 was responsible for the subsequent development of hyperthyroidism. It is only known that symptoms and signs of hyperthyroidism developed while the patient was receiving desiccated thyroid, and that no clear-cut manifestations of either hyperthyroidism or hypothyroidism existed prior to such therapy. The basis for the development of Graves' disease in patients who have previously received thyroid medication is not

understood. In those instances in which large amounts of thyroid are consumed and factitious hyperthyroidism develops, persistent thyroid overactivity after discontinuation of the hormone might be envisioned as a rebound phenomenon. During hormone therapy, TSH secretion presumably is suppressed, only to be followed by a period of hypersecretion of TSH when thyroid therapy is stopped. However, this mechanism does not account for all cases, since hyperthyroidism may also develop in patients taking only modest doses of thyroid and it may become apparent prior to discontinuing therapy, as in the present case. In either event, the hyperthyroidism initiated in this manner is frequently of the pituitarigenic type, associated with the early development of ophthalmopathy and other complications (1). This suggests that thyroid therapy upsets the control of TSH secretion in some manner.

Hyperthyroidism with the type of ophthalmopathy noted in this patient presents one of the most difficult therapeutic challenges in medical practice. It is generally believed that the ophthalmopathy is due to hypersecretion of TSH or of some as yet unidentified pituitary principle closely related to TSH. Measures designed to control the hyperthyroidism generally stimulate TSH secretion and, as a consequence, the eye manifestations may be increased. Ideally, therapy of such patients should be so designed as to allow for elasticity in management, depending on whether the hyperthyroidism or the ophthalmopathy represents the greater threat to the patient. Antithyroid drugs have the advantage that they can be discontinued should eye signs rapidly progress, but results with them have not generally been satisfactory. Radioiodine therapy has not been used extensively and has the same theoretical objection as subtotal thyroidectomy. The latter is equivalent to "burning one's bridges behind oneself." Paradoxically, however, an occasional case responds well to this treatment, but more often exophthalmos becomes worse postoperatively. This was true in the case under discussion. Radioiodine therapy deserves further trial in this syndrome. In our experience, the use of thyroid or of radiotherapy to the pituitary to suppress TSH secretion has not been notably successful, although in the present case the eyes symptoms did begin to subside after combined therapy was instituted, even though there was little or no change in the degree of exophthalmos. As one observes such patients, one wonders whether any therapeutic regimen designed to modify pituitary or thyroid function really influences the course of the ophthalmopathy, once it has been initiated. Perhaps the natural history of this malady is that it proceeds to a certain point and then regresses spontaneously. In some cases the process stops short of serious damage to the eye and in such cases success is apt to be credited to previous therapy.

In other cases the exophthalmos proceeds relentlessly and orbital decompression becomes imperative if the eye is to be saved.

The ophthalmopathy in this patient was unusual in that in addition to the usual findings of lid involvement, exophthalmos and ophthalmoplegia, there was a marked degree of optic neuritis. This is a rare complication, usually seen only in those patients in whom exophthalmos is extreme and in whom the eye is apt to be lost. Sattler, in his classic monograph on Basedow's disease, published in 1908 and reprinted in English in 1952, recorded optic neuritis both in patients with Graves' diseases and in those receiving desiccated thyroid, but it is uncertain whether these cases were uncomplicated by other diseases which might account for the optic neuritis (2).

Localized myxedema is considered to be a rare lesion, a recent report alleging that less than 100 cases have been reported in the literature up to 1949 (3). However, it has been known for a long time. Sattler describes a number of cases, including one reported by Basedow himself in 1840. It is our impression that it is probably much more common, particularly in its less dramatic forms, than has been generally suspected, largely because it is frequently overlooked. We have seen 5 cases in the past year, all in association with severe exophthalmos. In 3 of these, the skin and eye lesions developed during the stage of active hyperthyroidism. In the other 2, the skin lesions appeared after successful I^{131} therapy in one and after propylthiouracil therapy in the other. One patient had exophthalmos prior to antithyroid therapy and in the other it developed later. In 1 patient, the typical plaques were overlooked by five presumably competent observers, although the patient himself was aware of them but had not complained.

The pathologic physiology of localized myxedema is not well understood, but its frequent association with malignant exophthalmos suggests that both may have a common origin. Although not yet definitely proved, it is widely believed that thyrotropic hormone, or something closely related, plays a causative role in both syndromes. Watson and Pearce (4) have shown that there is an increase in the mucopolysaccharide content of the affected areas in pretibial myxedema, and Ludwig, *et al.* (5) have demonstrated an increase in water and hexosamine content of the orbital tissues of guinea pigs with TSH-induced exophthalmos. Hyaluronidase has been shown to be effective in converting the hard edema of localized myxedema to a pitting edema, as well as in decreasing experimental exophthalmos. In our patient, the involvement was so extensive that a trial of hyaluronidase therapy did not seem profitable. At the moment, there is no satisfactory treatment for this condition, but many of the reported cases

have improved spontaneously, sometimes after local trauma to the involved areas.

Clubbing of the fingers has been noted before, in association with this syndrome. Thomas published a striking example in 1933, designating it as acropachy (6). His patient had many features similar to those in the present case. X-ray examination revealed periosteal proliferation of a number of bones, including the terminal phalanges. Our patient likewise exhibited some periosteal proliferation of the distal phalanges upon x-ray examination in 1951.

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Editorial

METABOLIC PRECURSORS OF URINARY DEHYDROISOANDROSTERONE

EVER since dehydroisoandrosterone was first isolated from human urine in 1934 (1) the riddle of its precursor has plagued the biochemist and the clinician. Since it has recently been shown that dehydroisoandrosterone is excreted in normal urine in much larger amounts than hitherto recognized, and therefore that this substance is an important index of normal as well as abnormal adrenal cortical activity, the question of its precursor has assumed added importance. Especially is this true since the estimation of urinary dehydroisoandrosterone is probably as significant for evaluating adrenal cortical function as the determination of urinary corticoids.

It is unnecessary to dwell upon the reasons why earlier workers reported low excretion values (of the order of 0.2 mg. /day) (2) in the urine of normal men and women. It is well recognized now that vigorous acid hydrolysis alters a sensible fraction of the dehydroisoandrosterone sulfate present in any urine, resulting in an underestimation of the actual concentrations. Nevertheless a recent paper by Landau *et al.* (3) reported that normal men and women excreted 1.0–12.4 mg./twenty-four hours, or 10–60 per cent of the total ketosteroids, even when using a hydrolytic procedure consisting of boiling with acid for fifteen minutes. Dingemanse *et al.* (4) estimated from a chromatographic analysis of the urinary 17-ketosteroids that normal women excreted on the average 1.4 mg. of dehydroisoandrosterone daily (about 30 per cent of the total ketosteroids) and normal men, 2.6 mg. of the steroid daily (about 50 per cent of the total). Using a mild method of acid hydrolysis, Ronzoni (5) isolated the ketonic, digitonin-precipitable fraction and measured its dehydroisoandrosterone content by the Allen test (6). By this procedure she estimated the normal excretion of this adrenal metabolite to be 2.2–5.0 mg./twenty-four hours or 15–26 per cent of the total 17-ketosteroids.

Although attempts have been made to examine certain steroids as possible precursors of urinary dehydroisoandrosterone, the nature of these precursors remains obscure. In spite of the superficial similarity in chemical structure between the hormone, testosterone, and the metabolite, dehydroisoandrosterone, it was recognized early that the hormone was not the

precursor of the urinary steroid. The exogenous administration of huge doses of testosterone intramuscularly (7, 8) or intravenously (9) does not increase the concentration of urinary dehydroisoandrosterone.

There exists in the literature two conflicting statements regarding the precursor of dehydroisoandrosterone. Munson and co-workers (10) administered compounds E and F to adrenalectomized and gonadectomized men and found an increase in the excretion of dehydroisoandrosterone as measured by the Pettenkofer test. On the contrary, Wolfson *et al.* (11) reported that these two compounds did not augment the excretion of the Pettenkofer chromogen, although they found that corticosterone did. The bearing of these reports on the precursors of dehydroisoandrosterone must await the resolution of these opposing results and the determination of the exact nature of the chromogenic material.

Since the excretion of large amounts of dehydroisoandrosterone in the urine has always been found in association with adrenal hyperactivity, *e.g.*, following stimulation of the adrenals with ACTH (5, 12), the precursors of this metabolite must be sought among the steroids elaborated by the adrenal cortex. The exact chemical nature of this precursor, it seems to us, can be surmised from an examination of the chemical nature of some of the urinary steroids, together with a consideration of the mechanism of biogenesis of the adrenal hormones. A clue to the answer appears to rest with the Δ^5-3β-hydroxy grouping in rings A and B of the dehydroisoandrosterone molecule. In the past, attention has been focused upon the elucidation of a mechanism by which an active hormone, possessing as they all do an α,β-unsaturated carbonyl group in ring A, can be metabolized to the β,γ-unsaturated alcohol structure present in dehydroisoandrosterone. Although this conversion has recently been effected chemically, there is no evidence that this metabolic pathway exists in a living system. Indeed, a consideration of the variety of compounds that have been isolated from human urine which contain a Δ^5-3β-hydroxy system (Fig. 1) leads one to conclude that it is more likely that the immediate precursor of dehydroisoandrosterone is a substance containing such a chemical grouping. This consideration is not based solely on the number of such urinary steroids isolated but, more importantly, on the fact that they represent compounds reflecting different levels of the biogenetic and metabolic processes.

In addition to dehydroisoandrosterone (VII), the Hirschmanns (13–17) have isolated from the urine of a 7-year-old boy with carcinoma of the the adrenal cortex a number of Δ^5-3β-hydroxy steroids, among which were the C_{19}-compounds VIII and IX. Since the transformation of VII to VIII and IX has been shown to occur *in vitro* with liver slices by Schneider and Mason (18) it is likely that VIII and IX are also derived *in vivo* from VII; in any case, they provide little information concerning the precursor of

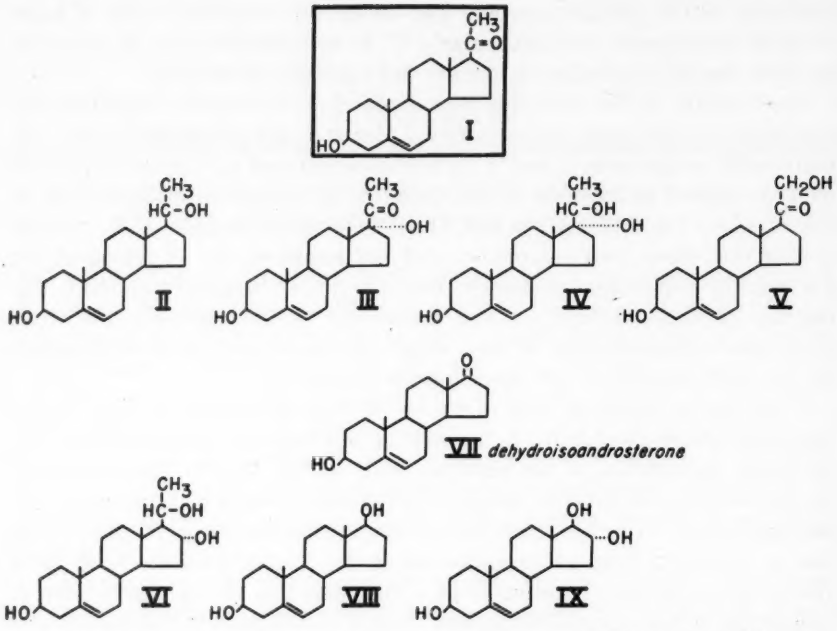

FIG. 1. Δ^5-Pregnenolone (I) and the Δ^5-3β-hydroxy steroids isolated from urine.

VII. From this same urine the Hirschmanns succeeded in isolating and identifying III (about 10 mg./liter) and IV (1.3 mg./liter), along with 315 mg./liter of dehydroisoandrosterone (VII). It was recognized by these workers, and has since been proved several times, that a C_{21}-steroid containing oxygen functions at C-17 and C-20 (such as III and IV) can be metabolically degraded to a C_{19}-17-ketone (such as VII). Administration of cortisone to humans has resulted in the increased excretion of 11-oxygenated 17-ketosteroids (19, 20) and recently Fukushima *et al.* (21) have reported the isolation of deutero-androsterone and deutero-etiocholanolone after the administration of isotopically labeled 17α-hydroxyprogesterone. Thus it seems possible that the immediate precursor(s) of dehydroisoandrosterone is a C_{21}-steroid containing oxygen functions on C-17 and C-20, as well as the Δ^5-3β-hydroxy system.

Compounds II and VI (6 mg./liter) were isolated by the Hirschmanns from the urine just described (14, 16). Compound II was also isolated by Miller and Dorfman (22) from the urine of a patient with adrenal hyperplasia (0.2 mg./liter) and by Marker and Rohrmann (23) from pregnant mares' urine. 21-Hydroxypregnenolone (V), probably a precursor of desoxycorticosterone, has been isolated from the urine only after the adminis-

tration of ACTH (24). Since these urinary metabolites, II, V and VI, do not possess the C-17 hydroxyl group it is unlikely that they give rise to dehydroisoandrosterone, for there is no evidence that C_{21}-pregnane derivatives without a tertiary hydroxyl group at C-17 can be transformed to 17-ketosteroids. But II, V and VI can provide information as to the nature of the precursor of VII, since they appear to us to represent urinary metabolites of *intermediates* in the biogenesis of the corticosteroids, compounds F and B. A brief discussion of the recent advances in the understanding of this biogenetic process will make this more evident. It has been demonstrated that the adrenal gland has the capacity to introduce hydroxyl groups into preformed steroids. Specifically, when progesterone was perfused through an isolated adrenal gland, Hechter *et al.* (25) isolated from the perfusate 11β-hydroxyprogesterone, 17α-hydroxyprogesterone, corticosterone (compound B) and hydrocortisone (compound F). When pregnenolone was added to the perfusate, progesterone, compound F and compound B were isolated. Thus, the reactions by which the adrenal gland can transform pregnenolone into compound F involve: oxidation of a Δ^5-3β-hydroxy group to a Δ^4-3-keto group (25, 26) and hydroxylation at C-11, at C-17 and at C-21. It is highly unlikely that all four of these reactions occur simultaneously and therefore a variety of intermediates can be produced. To account for the urinary steroids III, IV and V, it is merely necessary to assume that hydroxylation at C-17 and at C-21 can occasionally occur prior to the dehydrogenation of ring A. Thus, hydroxylation at C-17 of a properly constituted precursor(s) possessing the Δ^5-3β-ol group would yield III and IV, whereas hydroxylation at C-21 of the same precursor would give rise to V. Once removed from the environs of the adrenal gland these partially hydroxylated products may be further metabolized (*e.g.*, III→IV, or III→VII) and excreted into the urine. Therefore, it could be said that these substances as well as dehydroisoandrosterone (VII) are not the metabolites of a hormone but are the metabolites of an intermediate in the biosynthesis of the adrenal hormones.

The nature of this intermediate, it appears to us, is strongly suggested by the occurrence in the urine of Δ^5-pregnene-3β,20α-diol (II). The chemical nature of Δ^5-pregnenediol (II) as well as III, IV, V and the 16-hydroxylated compound,[1] VI, points directly to some compound structurally similar to these urinary steroids, possibly Δ^5-pregnene-3β-ol-20-one (I), as an *in vivo* intermediate in the synthesis of compounds B and F and as a pre-

[1] Hydroxylation at C-16, such as that found in VI and IX and also in estriol, androstane-3α,16α,17β-triol and etiocholane-3α,16α,17β-triol (27), is a transformation carried out in the liver (18) and probably is a step in the catabolism of the steroids leading to more highly degraded products. At present there is no indication that it is concerned with the biosynthesis of the steroid hormones.

cursor of urinary dehydroisoandrosterone. The fact that Δ^5-pregnenolone can be hydroxylated and serve as a precursor for the active hormones *in vitro* led Hechter *et al.* (25) to postulate that it was an *in vivo* precursor in corticosteroidogenesis. It may be noted that another authenticated *in vitro* precursor of compounds F and B, presumably via pregnenolone, is the Δ^5-3β-sterol, cholesterol. The Hirschmanns have already suggested that Δ^5-pregnenolone (I) is the metabolic precursor of II, for, despite the fact that I has not been isolated from adrenal extracts, two compounds which may be considered to be derived from it, progesterone and allopregnan-3β-ol-20-one, have been. Pregnenolone has been isolated by Ruzicka and Prelog (28) from pigs' testes. Whether Δ^5-pregnenolone is indeed this precursor remains to be proved by experiment.

The hypothesis that many urinary metabolites may be formed from adrenal intermediates rather than from active hormones, applies to normal persons as well as to those with adrenal disorders. Although many of the key intermediates which have been discussed have been isolated predominantly in those cases of adrenal hyperactivity in which excessive amounts of steroid metabolites appear in the urine, these intermediates reflect the processes which occur in the normal state. However, since this analysis has depended heavily upon a consideration of the steroids isolated from the urine of patients with adrenal disease, it is worthy of note that the deductions from this line of reasoning are in accord with some recent concepts of the pathogenesis of congenital adrenal hyperplasia. As Dr. Joseph Jailer has pointed out to us, the basic metabolic defect of this disease may be an inability of the adrenal gland to hydroxylate completely, especially at C-11. This results in an overproduction of androgenic substances such as 17α-hydroxyprogesterone or others which are responsible for the virilizing effects. As we have seen, such a defect, by giving rise to partially hydroxylated adrenal secretory products, such as the Δ^5-3β-ol intermediates, explains the occurrence of excessive amounts of II, III, IV, VII, VIII and IX in addition to others in the urine of such patients.

An extension of this approach can aid in the elucidation of the origin of other urinary metabolites. Thus, androsterone and etiocholanolone may be formed from 17α-hydroxyprogesterone, which may also be the progenitor of 17α-hydroxypregnan-3α-ol-20-one and 17α-hydroxypregnane-3α,20α-diol, both of which have been isolated from the urine of patients with adrenal hyperplasia or tumors (22, 29, 30, 31, 32). 11-Keto-pregnane-3α,20α-diol (33, 34) and 11-keto-pregnan-3α-ol-20-one (34) which have been isolated from human urine, could have arisen from an intermediate which was hydroxylated only at C-11. However, this may not be the sole source for such compounds, since Mason (33) has isolated 11-keto-pregnanediol after the administration of 11-dehydrocorticosterone (compound

A), indicating a metabolic pathway involving a conversion of a C-21 carbinol to a C-21 methyl group. The occurrence of excessive amounts of pregnane-3α,20α-diol in the urine of patients with adrenal hyperplasia and tumor (32) can be explained as arising from an adrenal precursor which escaped hydroxylation but underwent further oxidation and reduction, possibly in the liver or kidney. Pearlman and Pincus (35) have reported that the *in vivo* metabolism of Δ^5-pregnenolone resulted in the recovery of pregnanediol from the urine. The failure of Polley and Mason (36) and McGavack *et al.* (37) to find an increased excretion of 17-ketosteroids after the administration of pregnenolone has no bearing on the question of whether pregnenolone is a precursor of dehydroisoandrosterone or other 17-ketosteroids. The many alternate pathways that the administered pregnenolone could traverse before being presented to the adrenal gland for hydroxylation preclude any extensive conversion of this C-20 ketone to urinary 17-ketosteroids.

On the other hand, some 17-ketosteroids, especially androsterone and etiocholanolone, are derived from dehydroisoandrosterone itself, since it has been demonstrated (38, 39) that exogenously administered VII may be converted, probably via Δ^4-androstene-3,17-dione (or possibly testosterone), to androsterone and etiocholanolone. The metabolism of Δ^4-androstenedione, a compound which has been isolated from urinary (29) as well as adrenal extracts (40), has been shown by Dorfman *et al.* (41) to yield urinary androsterone and etiocholanolone.

It is clear from the foregoing discussion that in normal and diseased individuals urinary dehydroisoandrosterone can serve as an important index of the adrenal secretory process, since it is probably derived from the intermediates from which the active adrenal hormones, compounds F and B and desoxycorticosterone, are formed. Consideration of pregnenolone as one of the key steroidal intermediates from which these hormones as well as the Δ^5-3β-hydroxy urinary metabolites are formed, would serve to relate these metabolites, particularly dehydroisoandrosterone, to adrenal function.

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Questions and Answers

Questions submitted at the 1952 Postgraduate Assembly of the Endocrine Society

Answers by Ira T. Nathanson, Boston, Mass.

QUESTION: Please discuss the use of progesterone in breast cancer and as preoperative treatment in inoperable cervical cancer.

ANSWER: The effects of progesterone on breast cancer are equivocal. Random observations suggest apparent acceleration in some cases and evidence of regression in others. However, the natural variation of the disease makes it difficult to evaluate the significance of the responses. For a definitive answer, further studies are indicated. Combinations of progesterone with other steroids, particularly estrogens, have been tried. Here again, the cases are relatively few and the results cannot be interpreted.

There is as yet no concrete evidence that progesterone will convert an inoperable cancer of the cervix to an operable one. Modern concepts and techniques indicate that advanced lesions confined to the pelvis, previously considered inoperable, let alone incurable, are sometimes amenable to radical surgical attack. It appears that under the latter situation, some patients may obtain significant palliative benefit and in a relatively few instances may be rid of the disease. Possible effects of progesterone as a preoperative measure in such patients are extremely difficult to evaluate, essentially because of the inaccessibility of the disease for succinct study. Thus, at this time, no definite answer can be given, nor is it anticipated, unless methods for criteria of response are sharpened. For the most part, progesterone has been evaluated as a preoperative measure in those patients in whom the disease is relatively early and might be eradicated initially by radical surgery without pretreatment by progesterone. It has been stated that such lesions are made more susceptible to operative attack by progesterone, since they may undergo regression to a certain extent and the tissues surrounding the lesion are more easily dissected. This, too, needs further study.

QUESTION: Why is mastodynia often localized to upper outer quadrants?

ANSWER: If the breast is divided into true quadrants through the nipple, a major portion of the breast will be recognized in the upper outer segment. This anatomic entity may be the reason for the localization. This may also explain why the majority of benign and malignant lesions are found in this location. There is no other known explanation.

Answer by Ray F. Farquharson, Toronto, Canada

QUESTION: Is it not true that androgens are necessary in treating both males and females with panhypopituitarism?

ANSWER: Before the introduction of cortisone, both male and female patients suffering from severe anterior pituitary insufficiency (parahypopituitarism) were greatly helped by administration of testosterone in addition to desoxycorticosterone. The use of a

combination of cortisone (25 to 50 mg. per day) and desoxycorticosterone has been much more effective, however, the symptoms of adrenocortical insufficiency being almost completely relieved. In some cases the further addition of testosterone has appeared to increase the sense of well-being in women as well as in men but its actual role has yet to be determined.

Answer by Willard M. Allen, St. Louis, Missouri

QUESTION: Should castrates who have also had a hysterectomy be treated continuously with estrogen?

ANSWER: Patients who have had a hysterectomy and who are having menopausal symptoms can be treated continuously with estrogen.

Answer by R. L. Landau and A. T. Kenyon, Chicago, Ill.

QUESTION: What is the effect of cortisone or ACTH on seminal function? There are several reports of increased gonadotropin excretion following administration of these substances.

ANSWER: We know of no published results on the effects of cortisone, or of adrenal stimulation with ACTH, on spermatogenesis in man. However, Dr. Roger Baker of the Urology Department of the University of Chicago Clinics has observed 1 patient with azoospermia and 2 other patients with oligospermia from prolonged treatment with cortisone. In all instances normal seminal ejaculates were secured some two months after cortisone treatment was discontinued. Apparently the suppression of spermatogenesis, although it may be complete, is not permanent. This important question requires much further attention.

Answer by Rulon W. Rawson, New York, N. Y.

QUESTION: Parahydroxypropiophenone has been enthusiastically promoted by French workers in inhibiting TSH production. Some experiments performed in the United States do not confirm this work. Dr. Chavez in Mexico has found that in some cases there is a very good response and in others there is not. In 2 cases of my own it has failed to improve the patients. Please comment.

ANSWER: Studies carried out in American laboratories would indicate that parahydroxypropiophenone is neither able to inhibit the increased release of TSH by animals maintained on goiter-producing diets nor is it capable of preventing the production of TSH. This author does not know of anyone in this country who has obtained good results from the treatment of Graves' disease with this agent. This is in contrast to the observations made by certain French workers. With the data presently available, it is impossible to explain this discrepancy.

Answer by Paul Starr, Los Angeles, California

QUESTION: What is your opinion of iodinated thiourea derivatives?

ANSWER: Iodinated thiourea derivatives such as 5-iodo-thiouracil have proved to be very effective medications in the preparation of patients for the surgical treatment of thyrotoxicosis. For the prolonged medical treatment of hyperthyroidism they offer no advantage over noniodinated thiourea derivatives.

Answers by E. H. Rynearson, Rochester, Minn.

QUESTION: Would you use cortisone to treat a female diabetic with hirsutism?

ANSWER: Cortisone should not be given to such a patient for treatment but its use might be justified as a means of study. This question presupposes that both the diabetes and the hirsutism are caused by hyperfunction of the adrenal cortex (not proved) and that cortisone might be used to advantage to suppress this function. If the diabetes is caused by overproduction of a corticoid substance, then administration of cortisone should not be expected to alleviate it. Wilkins and his associates (1) reviewed the use of cortisone in the treatment of congenital hyperplasia of the adrenals. Sprague and his associates (2, 3) discussed the relationship of diabetes to the adrenal gland. Balfour and Sprague (2) described the association of diabetes mellitus with disorders of the anterior lobe of the pituitary body, the thyroid and the adrenal cortex.

A great need exists for further studies in this field and the physician who asked the question might contribute to our knowledge by studying the effect of administration of cortisone to patients such as he has mentioned.

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QUESTION: Discuss the relationship of hypoglycemia and "brain damage." How common?

ANSWER: Mild insulin reactions are common; they are becoming less frequent as physicians learn the use of newer types of insulin. Such reactions are not desirable, but neither, in so far as is known, do they produce any permanent damage to the brain; however, a severe hypoglycemic reaction may do so. Most investigators express the opinion that the symptoms of hypoglycemia are based on depression of oxidative processes in the brain, so that the cells are affected in the same manner as by anoxia from any cause. Evidence of this effect of hypoglycemia on the cells of the brain can be recorded electroencephalographically. These electro-encephalographic changes are nonspecific in nature and are similar to those seen in many other disorders producing a state of anoxia in the cells of the central nervous system. Fabrykant and co-workers (1, 2) published results of several recent studies that delve into the effects of hypoglycemia on the central nervous system in more detail than can be presented here.

Certain pathologic changes following severe insulin reactions have been noted at necropsies. These changes are strikingly similar to those seen in the brains of patients who die from the effects of cerebral anoxia. Hoff and co-workers (3), Wolf (4), and Moersch and Kernohan (5) stated that the most important of these changes are degeneration of the nerve cells and multiple petechial hemorrhages. Wolf (4) pointed out that early degenerative changes in the nerve cells, such as chromatolysis, as well as symptoms of hypoglycemia, are reversible if glucose is given early enough. If the hypoglycemic state persists long enough, certain irreversible or slowly reversible degenerative changes

may occur, resulting in necrosis and destruction of nerve cells and lack of relief of symptoms after intravenous administration of glucose.

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Answers by Laurance W. Kinsell, Oakland, California

QUESTIONS: Has x-ray therapy for acromegaly been given a fair chance in the past? One hears of good results with adequate doses.

ANSWER: The value of x-ray therapy in acromegaly is controversial. There is no question that it should always be used in the acromegalic patient who has a tumor which produces progressive pressure upon the optic nerve. In some of them at least, temporary improvement will result. Many people feel that extensive x-radiation should be used in all acromegalic patients.

Our own experience and opinions are as follows:

1. Many patients with acromegaly may be maintained in excellent condition for years with the use of estrogen and/or androgen for "inhibition of pituitary growth hormone production" (1).

2. X-radiation produces only very temporary arrest of the progress of acromegaly at best, and in many patients is almost completely ineffective.

3. In the analysis of a series of patients at the Massachusetts General Hospital who had received intensive x-radiation over a period of years, essentially no fall in the serum phosphorus level followed such treatment. Since the serum inorganic phosphorus level appears to be an index of growth hormone production in the nondiabetic acromegalic, this would further indicate the inadequacy of radiation therapy.

1. Kinsell, Laurance W.; Michaels, George D.; Li, Choh Hao, and Larsen, William E.: Studies in growth. I. Interrelationship between pituitary growth factor and growth-promoting androgens in acromegaly and gigantism. II. Quantitative evaluation of bone and soft tissue growth in acromegaly and gigantism, *J. Clin. Endocrinol.* **8:** 1013, 1948.

QUESTION: Why does the acromegalic have polydipsia and polyuria?

ANSWER: The question as stated implies that polydipsia and polyuria are usually found in acromegalic patients. In our experience, they represent relatively uncommon findings.

Polyuria, with consequent polydipsia, can result from any condition which will interfere with normal reabsorption of water by the kidney tubules, the two most common endocrine conditions being diabetes mellitus and diabetes insipidus. In diabetes mellitus glycosuria is responsible for the excessive water loss and the condition is corrected by insulin. In diabetes insipidus, one is dealing with impaired production of antidiuretic hormone by the posterior pituitary. Glycosuria, in association with insulin-resistant

diabetes, is commonly associated with acromegaly. It is usually of mild degree but, when severe, can readily cause polyuria and polydipsia. Diabetes insipidus is very rarely associated with acromegaly.

Answer by Francis D. W. Lukens, Philadelphia, Pa.

QUESTION: In an obese diabetic with glycosuria, not taking insulin, is insulin needed when a reducing diet is not accomplishing its purpose? Will obesity be further increased by the addition of insulin?

ANSWER: The first question requires some explanation. If the reducing diet is not accomplishing its purpose (of controlling the diabetes) because it is not adhered to, it is logical to continue the efforts at education and adjustment of the patient, without insulin, provided there are no major symptoms or complications which demand immediate care. If the diet is not accomplishing the control of diabetes in spite of initial weight loss, the patient probably will need insulin. The exact time to begin insulin is a matter of opinion. There appear to be two components in the control of the obese diabetic by diet: (a) the immediate reduction in food intake which renders the urine sugar-free within a week as a rule, before there is significant weight loss, and (b) the beneficial effect of weight loss which, in the well behaved patient, is added to the foregoing over a period of months. It is logical to work for weight loss before starting insulin; it is also appropriate at times to protect the ignorant patient from uncontrolled symptoms, and from present or potential complications, by using insulin without waiting for weight loss.

In answer to the second question, obese patients who take insulin will not gain weight, but they rarely lose weight. This is due to difficulty (?) or lack of cooperation in the use of a reducing diet. It is not due to a powerful effect of insulin, if one may judge by the modest results when insulin is given to thin people to promote gain in weight.

Answer by Samuel F. Haines, Rochester, Minn.

QUESTION: If Graves' disease is often associated with oligomenorrhea, why is thyroid used in the treatment of oligomenorrhea?

ANSWER: Actually, I know of no good evidence that Graves' disease is often associated with oligomenorrhea. Some individuals who have constitutionally low basal metabolic rates, without evidence of thyroid deficiency, have oligomenorrhea; following the administration of desiccated thyroid normal menstruation sometimes ensues. There is no reason in these individuals to assume that any disturbance of thyroid function exists, or that the effect of the administration of thyroid is specific in any sense of the word. Neither is there good evidence to indicate the nature of its action. It is probably true that it does have some influence which helps in the re-establishment of normal menstruation in such cases. Patients with true myxedema, who have menstrual disturbances, are more likely to have excessive menstruation than any other change.

Answer by C. L. Buxton, New York, N. Y.

QUESTION: Please comment on the cervical mucus test for pregnancy (test of Dr. Roland).

ANSWER: It is assumed that this test is the one which is based on the presence or absence of fern-like crystallization of mucus, when the smear is dry. This test has been described by Rydberg of Copenhagen and Da Paz of Brazil and is an indication that there is a

change in the variety of crystallization of cervical mucus as a result of estrogen secretion by the organism. Having had no personal experience with this test, I do not think I can make an authoritative statement in connection with it except to say that, although it may be valuable for the negative diagnosis of pregnancy, the probabilities are that there are so many other hormonal activities of a steroid character which might simulate those of early pregnancy, that the test probably has doubtful validity as a positive diagnosis of this condition.

Answers by John E. Howard, Baltimore, Md.

QUESTION: How do you explain gynecomastia in persons who, after starvation, start eating well?

ANSWER: I have never heard any fully satisfactory explanation given. The least unsatisfactory has seemed that after severe starvation refeeding provides either the pituitary or the gonads with building blocks such that there is an earlier functional return of estrogen production than of androgen. It seems unlikely that the hepatic dysfunction which accompanies severe malnutrition is the chief factor in the gynecomastia (by failure to "detoxify" a normal estrogen production), but others may well disagree. For example, Klinefelter (1) is of the opinion that the liver damage, plus B-complex deficiency, resulting from starvation prevents for a while the glycuronidation of estrogens which are produced early in the recovery phase.

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QUESTION: What do you think of the strumitis produced by "trepanosoma cruzi?"

ANSWER: I have had no experience with this disease. Oxford Medicine says: "The view that a form of endemic goitre is caused by T. cruzi is now generally abandoned, its basis, coexistence in the same patient, being due to geographical coincidence. T. cruzi is found rarely in the thyroid either in man or infected animals."

QUESTION: The relation of exophthalmic goiter and myasthenia gravis seems rare indeed, yet some authors stress relationship. Please comment.

ANSWER: So far as we are aware, no etiologic relationship between myasthenia gravis and Graves' disease has ever been demonstrated. In both diseases there is apt to be manifest weakness, especially of the extracellular muscles; and in the so-called myopathic type of thyrotoxicosis (1), muscle atrophy and weakness may be such prominent features as to suggest myasthenia gravis. Clearly then, in a patient with myasthenia gravis the concomitant existence of thyrotoxicosis would greatly exaggerate the muscular weakness and should always be sought, since if the thyrotoxicosis is overcome there will likely be great improvement in the myasthenia, as has been shown by Thorn (2). The muscular weakness of thyrotoxicosis is little if any benefited by prostigmine.

1. Zierler, K. L.: Muscular wasting of obscure origin and the thyroid gland, *Bull. Johns Hopkins Hosp.* **89**: 263, 1951.
2. Thorn, G. W., and Tierney, N. A.: Myasthenia gravis complicated by thyrotoxicosis: creatine studies, *Bull. Johns Hopkins Hosp.* **69**: 469, 1941.

The Endocrine Society

THE SIXTH ANNUAL POSTGRADUATE ASSEMBLY IN ENDOCRINOLOGY AND METABOLISM

SPONSORED JOINTLY BY THE ENDOCRINE SOCIETY AND THE UNIVERSITY OF MINNESOTA AT THE CENTER FOR CONTINUATION STUDY OF THE UNIVERSITY OF MINNESOTA MEDICAL SCHOOL, MINNEAPOLIS, MINNESOTA

September 28–October 3, 1953

The faculty will consist of fifteen clinicians and investigators eminently qualified in the fields of endocrinology and metabolism. The program will consist of lectures, demonstrations of laboratory tests, presentation of cases, and question and answer panel discussions.

The forty-five lectures to be presented will cover most of the phases of endocrinology and certain metabolic diseases. The course is designed to give a broad basis of understanding of diagnosis and therapy in the field of endocrinology and metabolism for the man in general practice and for those in other specialties who wish to have a general knowledge of this rapidly growing field.

A syllabus with brief abstracts of the lectures will be available to the registrants at the time of the Assembly.

For further information concerning the program, write to the Director, Center for Continuation Study, University of Minnesota, Minneapolis 14, Minnesota. Arrangements for housing accommodations will be made through the Center for Continuation Study. Tuition fee, $100.00.

(For *program*, see the July issue of the Journal.)

THE 1954 ANNUAL MEETING

The next Annual Meeting of the Endocrine Society will be held in the Sir Francis Drake Hotel, San Francisco, California, June 17, 18 and 19, 1954.

The American Goiter Association

THE 1954 ANNUAL MEETING

The next Annual Meeting of the American Goiter Association will be held in the Hotel Somerset, Boston, Massachusetts, April 29, 30 and May 1, 1954.

VAN METER PRIZE AWARD FOR 1954

The American Goiter Association again offers the Van Meter Prize Award of Three Hundred Dollars and two honorable mentions for the best essays submitted concerning original work on problems related to the thyroid gland. The award will be made at the annual meeting of the Association which will be held in Boston, Massachusetts, April 29, 30 and May 1, 1954, providing essays of sufficient merit are presented in competition.

The competing essays may cover either clinical or research investigations; should not exceed three thousand words in length; must be presented in English, and a typewritten double-spaced copy in duplicate sent to the Corresponding Secretary, Dr. John C. McClintock, 149½ Washington Avenue, Albany 10, New York, not later than *January 15, 1954*. The committee, who will review the manuscripts, is composed of men well qualified to judge the merits of the competing essays.

A place will be reserved on the program of the annual meeting for the presentation of the Prize Award Essay by the author, if it is possible for him to attend. The essay will be published in the annual Transactions of the Association.